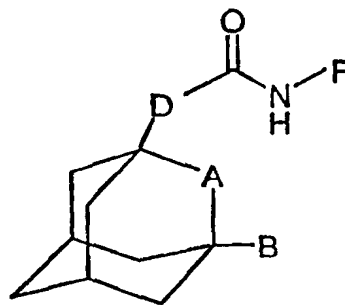




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(21) International Application Number: PCT/SE98/02189 (22) International Filing Date: 1 December 1998 (01.12.98) (30) Priority Data: 9704545-4 5 December 1997 (05.12.97) SE (71) Applicant (for all designated States except MG US): ASTRA PHARMACEUTICALS LTD. [GB/GB]; Home Park, Kings Langley, Herts WD4 8DH (GB). (71) Applicant (for MG only): ASTRA AKTIEBOLAG [SE/SE]; S-151 85 Södertälje (SE). (72) Inventors; and (75) Inventors/Applicants (for US only): BAXTER, Andrew [GB/GB]; Astra Charnwood, Bakewell Road, Loughborough, Leics. LE11 5RH (GB). BROUGH, Stephen [GB/GB]; Astra Charnwood, Bakewell Road, Loughborough, Leics. LE11 5RH (GB). MCINALLY, Thomas [GB/GB]; Astra Charnwood, Bakewell Road, Loughborough, Leics. LE11 5RH (GB). MORTIMORE, Michael [GB/GB]; Astra Charnwood, Bakewell Road, Loughborough, Leics. LE11 5RH (GB). CLADINGBOEL, David		[GB/GB]; Astra Charnwood, Bakewell Road, Loughborough, Leics. LE11 5RH (GB). (74) Agent: ASTRA AKTIEBOLAG; Intellectual Property, Patents, S-151 85 Södertälje (SE). (81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>
(54) Title: ADAMANTANE DERIVATIVES (57) Abstract The invention provides adamantane derivatives represented by formula (I), a process for their preparation, pharmaceutical compositions containing them, a process for preparing the pharmaceutical compositions, and their use in therapy. In said formula (I), A represents a group CH ₂ or an oxygen atom; B represents a hydrogen or halogen atom; D represents a group CH ₂ , OCH ₂ , NHCH ₂ or CH ₂ CH ₂ ; R represents a phenyl, benzothiazolyl, indolyl, indazolyl, purinyl, pyridyl, pyrimidinyl or thiophenyl group, each of which may be optionally substituted by one or more substituents.		



(I)

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AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
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ADAMANTANE DERIVATIVES

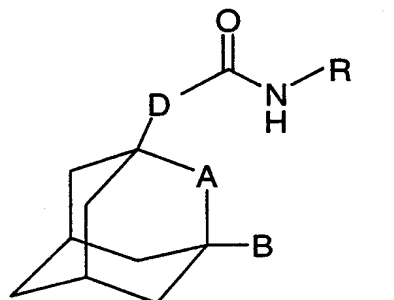
The present invention relates to adamantane derivatives, a process for their preparation, pharmaceutical compositions containing them, a process for preparing the pharmaceutical compositions, and their use in therapy.

Adamantane derivatives are known in the art, e.g. from US-A-3,789,072 as serotonin inhibitors, from Chem. Abs. (1974), Vol. 80, No.5 (26871m) as inflammation and edema inhibitors or analgesics, from Chem. Abs. (1975), Vol. 82, No.1 (3853j) and Chem. Abs. (1977), Vol. 86, No.17 (120855e) as antiviral agents, and also from Chem. Abs. (1968), Vol. 69, No.1 (2562h), Chem. Abs. (1975), Vol. 82, No.3 (16510v) and Tetrahedron (1988), 44, No. 23, 7234-7242.

The P2X₇ receptor (previously known as P2Z receptor), which is a ligand-gated ion channel, is present on a variety of cell types, largely those known to be involved in the inflammatory/immune process, specifically, macrophages, mast cells and lymphocytes (T and B). Activation of the P2X₇ receptor by extracellular nucleotides, in particular adenosine triphosphate, leads to the release of interleukin-1 β (IL-1 β) and giant cell formation (macrophages/microglial cells), degranulation (mast cells) and L-selectin shedding (lymphocytes). P2X₇ receptors are also located on antigen-presenting cells (APC), keratinocytes, salivary acinar cells (parotid cells) and hepatocytes.

It would be desirable to make compounds effective as P2X₇ receptor antagonists for use in the treatment of inflammatory, immune or cardiovascular diseases, in the aetiologies of which the P2X₇ receptor may play a role.

In accordance with the present invention, there is therefore provided a compound of general formula



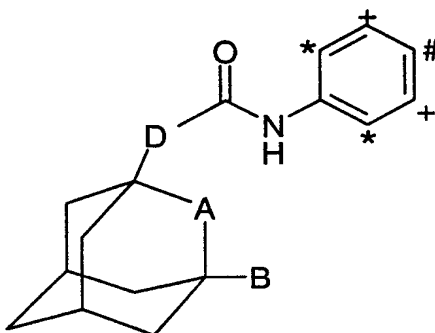
(I)

- wherein A represents a group CH₂ or an oxygen atom; B represents a hydrogen or
 5 halogen atom (e.g. fluorine, chlorine, iodine and especially bromine);
 D represents a group CH₂, OCH₂, NHCH₂ or CH₂CH₂, in particular a group CH₂,
 OCH₂ or NHCH₂;
 R represents a phenyl, benzothiazolyl, indolyl, indazolyl, purinyl, pyridyl, pyrimidinyl or
 thiophenyl group, each of which may be optionally substituted by one or more substituents
 10 independently selected from a halogen atom or a cyano, carboxyl, hydroxyl, nitro,
 halo-C₁-C₆-alkyl, -N(R¹)-C(=O)-R², -C(O)NR³R⁴, -NR⁵R⁶, C₃-C₈-cycloalkyl,
 3- to 8-membered heterocyclyl, C₃-C₈-cycloalkyloxy, C₁-C₆-alkylcarbonyl, phenoxy,
 benzyl, C₁-C₆-alkylthio, phenylthio, C₁-C₆-alkoxycarbonyl, C₁-C₆-alkylsulphinyl or
 C₁-C₆-alkylsulphonyl group, or a C₁-C₆-alkyl or C₁-C₆-alkoxy group optionally
 15 substituted by one or more substituents independently selected from a halogen atom or an
 amino, carboxyl, hydroxyl, C₁-C₆-alkoxy, (di)C₁-C₆-alkylamino,
 C₁-C₆-alkoxycarbonyl, imidazolyl, morpholinyl, piperidinyl or pyrrolidinyl group;
 R¹ represents a hydrogen atom or a C₁-C₆-alkyl or C₃-C₈-cycloalkyl group;
 R² represents a C₁-C₆-alkyl or C₃-C₈-cycloalkyl group; and
 20 R³, R⁴, R⁵ and R⁶ each independently represent a hydrogen atom or a C₁-C₆-alkyl or
 C₃-C₈-cycloalkyl group;
 with the provisos that when A is CH₂, B is H and D is CH₂, then R does not represent a
 phenyl, ortho-carboxyphenyl, methylphenyl or para-phenoxyphenyl group, and that when A
 is CH₂, D is CH₂ or CH₂CH₂ and R represents a substituted phenyl group, the
 25 substituent or substituents present do not comprise, in an ortho position, a C₁-C₆-alkoxy

group substituted by an amino, (di)C₁-C₆-alkylamino, imidazolyl, morpholinyl, piperidinyl or pyrrolidinyl group;

or a pharmaceutically acceptable salt or solvate thereof.

In the context of the present specification, unless otherwise indicated, an alkyl substituent or alkyl moiety in a substituent group may be linear or branched. Furthermore, the (cyclo)alkyl moieties in a dialkylamino, dicycloalkylamino, dialkylamido or dicycloalkylamido substituent group may be the same or different. When D represents a group OCH₂ or NHCH₂, the group is orientated such that the oxygen or nitrogen atom is directly attached to the adamantyl group. A 3- to 8-membered heterocyclyl group should be understood to mean an aliphatic heterocyclic ring system containing a single heteroatom selected from nitrogen, oxygen or sulphur. The term "in an ortho position" defines the ring position on the phenyl ring of R which is adjacent to the point of attachment of the amide linking group to R, e.g., as illustrated in the formula below where the asterisks define the "ortho position":



Similarly, meta and para positions in the phenyl group R are defined relative to the point of attachment of the amide linking group to R and are indicated in the above formula by the symbols + and # respectively.

Preferably, R represents a phenyl, benzothiazolyl, indolyl, indazolyl, purinyl, pyridyl, pyrimidinyl or thiophenyl group, each of which may be optionally substituted by one, two, three or four substituents independently selected from a halogen atom (e.g. fluorine, chlorine, bromine or iodine) or a cyano, carboxyl, hydroxyl, nitro, halo-C₁-C₆-alkyl (e.g. trifluoromethyl), -N(R¹)-C(=O)-R², -C(O)NR³R⁴, -NR⁵R⁶, C₃-C₈-cycloalkyl (e.g. cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl), 3- to 8-membered heterocyclyl (e.g.

aziridinyl, pyrrolidinyl, piperidinyl), C₃-C₈-cycloalkyloxy (e.g. cyclopropyloxy, cyclobutyloxy, cyclopentyloxy or cyclohexyloxy), C₁-C₆-alkylcarbonyl (e.g. methyl-, ethyl-, propyl-, butyl-, pentyl- or hexylcarbonyl), phenoxy, benzyl, C₁-C₆-alkylthio (e.g. methyl-, ethyl-, propyl-, butyl-, pentyl- or hexylthio), phenylthio, C₁-C₆-alkoxycarbonyl (e.g. methoxy-, ethoxy-, propoxy-, butoxy-, pentoxy- or hexoxycarbonyl), C₁-C₆-alkylsulphinyl (e.g. methyl-, ethyl-, propyl-, butyl-, pentyl- or hexylsulphinyl), or C₁-C₆-alkylsulphonyl (e.g. methyl-, ethyl-, propyl-, butyl-, pentyl- or hexylsulphonyl) group, or a C₁-C₆-alkyl (e.g. methyl, ethyl, propyl, butyl, pentyl or hexyl) or C₁-C₆-alkoxy (e.g. methoxy-, ethoxy-, propoxy-, butoxy-, pentoxy- or hexoxy) group optionally substituted by one, two, three or four substituents independently selected from a halogen atom (e.g. fluorine, chlorine, bromine or iodine) or an amino, carboxyl, hydroxyl, C₁-C₆-alkoxy (e.g. methoxy, ethoxy, propoxy, butoxy, pentoxy or hexoxy), (di)C₁-C₆-alkylamino (e.g. (di)methylamino or (di)ethylamino), C₁-C₆-alkoxycarbonyl (e.g. methoxy-, ethoxy-, propoxy-, butoxy-, *tert*-butoxy-, pentoxy- or hexoxycarbonyl),, imidazolyl, morpholinyl, piperidinyl or pyrrolidinyl group.

More preferably, R represents a phenyl, benzothiazolyl, indolyl, indazolyl, purinyl, pyridyl or thiophenyl group, each of which may be optionally substituted by one, two or three substituents independently selected from a halogen atom (especially chlorine) or a hydroxyl, nitro or C₁-C₄-alkoxycarbonyl (in particular methoxycarbonyl) group, or a C₁-C₄-alkyl (most preferably C₁-C₂-alkyl) or C₁-C₄-alkoxy (most preferably C₁-C₃-alkoxy) group optionally substituted by one or two substituents independently selected from a halogen atom or an amino, carboxyl, hydroxyl, C₁-C₄-alkoxy (especially methoxy), (di)C₁-C₄-alkylamino (in particular methylamino or dimethylamino), C₁-C₄-alkoxycarbonyl (especially *tert*-butoxycarbonyl), imidazolyl, morpholinyl, piperidinyl or pyrrolidinyl group.

It is preferred that R¹ represents a hydrogen atom or a C₁-C₄-alkyl (e.g. methyl, ethyl, propyl or butyl) or C₃-C₆-cycloalkyl (e.g. cyclopentyl or cyclohexyl) group.

Preferably R² represents a C₁-C₄-alkyl (e.g. methyl, ethyl, propyl or butyl) or C₃-C₆-cycloalkyl (e.g. cyclopentyl or cyclohexyl) group.

Preferably, R³, R⁴, R⁵ and R⁶ each independently represent a hydrogen atom or a C₁-C₄-alkyl (e.g. methyl, ethyl, propyl or butyl) or C₃-C₆-cycloalkyl (e.g. cyclopentyl or cyclohexyl) group.

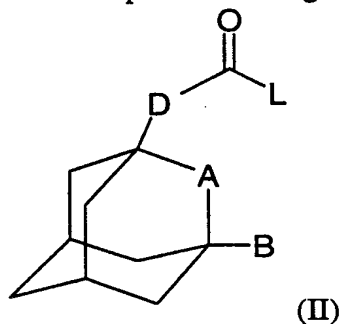
Preferred compounds of the invention include:

- 5 *N*-(2-Methyl-6-benzothiazolyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
N-(3-(3-(Aminopropoxy)-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
hydrochloride,
N-(2-Chlorophenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
N-(2,4,5-Trimethylphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
10 *N*-(5-Methoxy-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
N-(2,3-Dimethylphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
N-(5-Indolyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
N-(2,3-Dimethyl-5-indolyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
N-[5-(3-*N,N*-Dimethylaminopropoxy)-2-methylphenyl]-tricyclo[3.3.1.1^{3,7}]decane-1-
15 acetamide, hydrochloride,
N-(5-Indazolyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
N-(6-Indazolyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
N-(5-Hydroxy-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
N-(1*H*-Indol-4-yl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
20 4-Methyl-3-[[1-oxo-2-(tricyclo[3.3.1.1^{3,7}]dec-1-yl)ethyl]amino]phenoxy-acetic acid,
hydrochloride salt,
N-(1-Methyl-1*H*-indol-5-yl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
N-(1-(*N,N*-Dimethylamino)ethyl-1*H*-indo-5-yl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
5-[[1-Oxo-2-(tricyclo[3.3.1.1^{3,7}]dec-1-yl)ethyl]amino]-1*H*-indole-1-acetic acid,
25 1,1-dimethylethyl ester,
N-(3-(2-Chloropyridyl))-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
N-(3-(*N,N*-Dimethylamino)methyl-1*H*-indo-5-yl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
N-(4-Methoxy-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
N-(2-Chloro-5-methoxyphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
30 *N*-(4-Hydroxy-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,

- N*-(3-Hydroxymethyl-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
N-(5-Methoxy-2-methyl-3-nitrophenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
N-(5-Hydroxymethyl-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
N-(3-Hydroxy-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
5 *N*-(2-Methyl-5-(1-pyrrolidinemethyl)phenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
hydrochloride,
N-(2-Chloro-5-hydroxyphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
N-(2-Chloro-4-hydroxyphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
N-(2-Methyl-3-(2-(1-pyrrolidino)ethyloxy)phenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
10 hydrochloride,
N-(5-Methoxymethyl-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
N-(2-Methyl-3-(2-(1-morpholino)ethyloxy)phenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
hydrochloride,
N-(2-Methyl-3-(2-(1-piperidino)ethyloxy)phenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
15 hydrochloride,
N-(2-Methyl-5-(1-morpholinomethyl)phenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
hydrochloride,
N-(5-(3-(2-*N,N*-dimethylaminoethyl)indolyl))-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
hydrochloride,
20 Methyl 4-methyl-3-[[1-oxo-2-(tricyclo[3.3.1.1^{3,7}]dec-1-yl)ethyl]amino]thiophene-2-
carboxylate,
N-(3-Methoxy-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
N-(2-Methyl-3-(2-(1-imidazolo)ethyloxy)phenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
N-(2,4,6-Trimethylphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
25 *N*-(5-(3-Aminopropoxy)-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
hydrochloride,
N-(5-(3-(*N*-Methylamino)propoxy)-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-
acetamide, hydrochloride,
*N*6-(Tricyclo[3.3.1.1^{3,7}]decane-1-acetyl)adenine,
30 *N*-(3,5-Dimethoxy-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,

- N*-(3-(3-(*N*-Methylamino)propyloxy)-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide, hydrochloride,
- N*-(5-(3-(*N,N*-Dimethylamino)propyloxy)-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide, hydrochloride,
- 5 *N*-(5-Methoxy-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decanyloxy-1-acetamide,
- N*-(5-Methoxy-2-methylphenyl)-(3-bromo-tricyclo[3.3.1.1^{3,7}]decane)-1-acetamide,
- N*-(5-Methoxy-2-methylphenyl)-(2-oxa-tricyclo[3.3.1.1^{3,7}]decane)-1-acetamide,
- N*-(5-Methoxy-2-methylphenyl)-2-(tricyclo[3.3.1.1^{3,7}]decan-1-amino)acetamide,
- N*-(3,5-Dimethoxyphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
- 10 *N*-(3,5-Dihydroxyphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
- N*-(3,5-Dimethoxyphenyl)-tricyclo[3.3.1.1^{3,7}]decanyloxy-1-acetamide,
- N*-(3,5-Bis-(3-aminopropyloxy)phenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
- N*-(2,4,5-Trimethylphenyl)-tricyclo[3.3.1.1^{3,7}]decanyloxy-1-acetamide,
- N*-(5-Hydroxy-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decanyloxy-1-acetamide,
- 15 *N*-(5-(2-(*N*-Methylamino)ethyloxy)-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide, hydrochloride,
- N*-(5-(2-(*N*-Methylamino)ethyloxy)-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decanyloxy-1-acetamide,
- N*-(5-(3-(*N*-Methylamino)propyloxy)-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decanyloxy-1-
- 20 acetamide, and
- N*-(3,5-Dihydroxy-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decane-acetamide.

The present invention further provides a process for the preparation of a compound of formula (I) as defined above which comprises reacting a compound of general formula



wherein L represents a leaving group (e.g. a halogen atom such as chlorine or an imidazole group) and A, B and D are as defined in formula (I), with a compound of general formula (III), R-NH₂, wherein R is as defined in formula (I); and optionally forming a pharmaceutically acceptable salt or solvate thereof.

5 The process may conveniently be carried out in a solvent (e.g. acetonitrile, *N,N*-dimethylformamide or dichloromethane) and optionally in the presence of a base (e.g. triethylamine, 4-dimethylaminopyridine or diisopropylethylamine). The process is conveniently operated at a temperature in the range from 0 to 100 °C, preferably in the range from 10 to 80 °C, and especially at ambient temperature (20 °C).

10 The compounds of formula (II) and (III) are known compounds or may be prepared by processes analogous to those known in the art.

It will be appreciated by those skilled in the art that in the process of the present invention certain functional groups such as hydroxyl or amino groups in the intermediate compounds may need to be protected by protecting groups. Thus, the final stage in the
15 preparation of the compounds of formula (I) may involve the removal of one or more protecting groups.

The protection and deprotection of functional groups is described in 'Protective Groups in Organic Chemistry', edited by J.W.F. McOmie, Plenum Press (1973) and 'Protective Groups in Organic Synthesis', 2nd edition, T.W. Greene and P.G.M. Wuts,
20 Wiley-Interscience (1991).

The compounds of formula (I) above may be converted to a pharmaceutically acceptable salt or solvate thereof, preferably an acid addition salt such as a hydrochloride, hydrobromide, phosphate, acetate, fumarate, maleate, tartrate, citrate, oxalate, methanesulphonate or *p*-toluenesulphonate, or an alkali metal salt such as a sodium or
25 potassium salt.

Certain compounds of formula (I) are capable of existing in stereoisomeric forms. It will be understood that the invention encompasses all geometric and optical isomers of the compounds of formula (I) and mixtures thereof including racemates. Tautomers and mixtures thereof also form an aspect of the present invention.

The compounds of the present invention are advantageous in that they possess pharmacological activity. They are therefore indicated as pharmaceuticals for use in the treatment or prevention of rheumatoid arthritis, osteoarthritis, psoriasis, allergic dermatitis, asthma, hyperresponsiveness of the airway, septic shock, glomerulonephritis, irritable
5 bowel disease, Crohn's disease, ulcerative colitis, atherosclerosis, growth and metastases of malignant cells, myocardial ischaemia, myoblastic leukaemia, diabetes, Alzheimer's disease, osteoporosis, burn injury, stroke, varicose veins and meningitis.

Accordingly, the present invention provides a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined for use in
10 therapy.

In another aspect, the invention provides the use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined in the manufacture of a medicament for use in therapy.

The invention further provides a method of effecting immunosuppression (e.g. in the
15 treatment of rheumatoid arthritis, irritable bowel disease, atherosclerosis or psoriasis) which comprises administering a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined to a patient.

For the above-mentioned therapeutic uses the dosage administered will, of course,
20 vary with the compound employed, the mode of administration, the treatment desired and the disorder indicated.

The compounds of formula (I) and pharmaceutically acceptable salts and solvates thereof may be used on their own but will generally be administered in the form of a pharmaceutical composition in which the formula (I) compound/salt/solvate (active
25 ingredient) is in association with a pharmaceutically acceptable adjuvant, diluent or carrier. Depending on the mode of administration, the pharmaceutical composition will preferably comprise from 0.05 to 99 %w (per cent by weight), more preferably from 0.10 to 70 %w, of active ingredient, and, from 1 to 99.95 %w, more preferably from 30 to 99.90 %w, of a pharmaceutically acceptable adjuvant, diluent or carrier, all percentages by weight being
30 based on total composition.

Thus, the present invention also provides a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined in association with a pharmaceutically acceptable adjuvant, diluent or carrier.

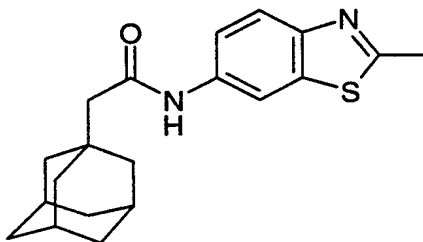
5 The invention further provides a process for the preparation of a pharmaceutical composition of the invention which comprises mixing a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined with a pharmaceutically acceptable adjuvant, diluent or carrier.

The pharmaceutical composition of the invention may be administered topically (e.g. 10 to the lung and/or airways or to the skin) in the form of solutions, suspensions, heptafluoroalkane aerosols and dry powder formulations; or systemically, e.g. by oral administration in the form of tablets, capsules, syrups, powders or granules, or by parenteral administration in the form of solutions or suspensions, or by subcutaneous administration or by rectal administration in the form of suppositories or transdermally.

15 The present invention will be further understood by reference to the following illustrative examples in which the terms MS, NMR, CDCl_3 and DMSO denote respectively mass spectrometry, nuclear magnetic resonance, chloroform-*d* and dimethylsulphoxide.

Example 1

20 *N*-(2-Methyl-6-benzothiazolyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide



a) 1-Adamantaneacetyl chloride

A solution of 1-adamantaneacetic acid (4.5 g) in thionyl chloride (20 ml) was heated at reflux temperature for 24 hours and then allowed to cool to ambient temperature. The 25 excess thionyl chloride was removed under reduced pressure to leave the sub-title compound as a syrup (4.9 g).

b) *N*-(2-Methyl-6-benzothiazolyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide

To a solution of 1-adamantaneacetyl chloride (0.5 g) prepared as described in a) above in acetonitrile (10 ml) was added triethylamine (0.38 ml) and 6-amino-2-methylbenzothiazole (0.39 g). The reaction mixture was stirred at ambient temperature for 1 hour before being diluted with ethyl acetate. The organic phase was then washed with dilute hydrochloric acid and water, dried over magnesium sulphate (MgSO₄) and finally concentrated under reduced pressure to give the title compound as a white solid (0.12 g).

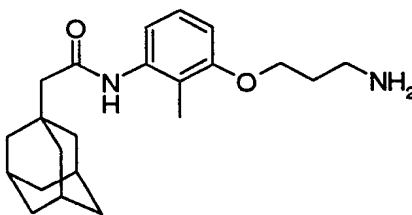
Melting point: 172 °C

MS (APCI +ve) 341 (M+H)⁺

¹H NMR (CDCl₃) δ 8.45 (1H, d), 7.84 (1H, d), 7.19 (2H, m), 2.81 (3H, s), 2.13 (2H, s), 2.00 (3H, s), 1.75 (12H, m)

Example 2

***N*-(3-(3-(Aminopropoxy)-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide, hydrochloride**



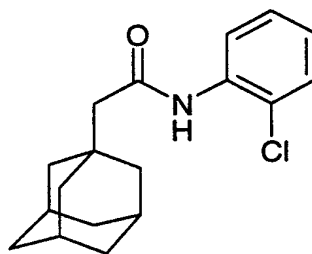
methanol (10 ml) at 0°C **CARE - Very Exothermic**) was then added to the latter solution and the reaction stirred at room temperature for 2 hours. The reaction was partitioned between saturated aqueous sodium hydrogen carbonate (100 ml) and extracted with ethyl acetate (100 ml). The organic extract was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with dichloromethane : ethanol : triethylamine (18:2:1) to give a yellow oil. The latter was dissolved in methanol (10 ml) and dichloromethane (2 ml) and treated with an ethereal solution of hydrogen chloride (1M, 5 ml). After 2 minutes the solvents were removed under reduced pressure. The residual gum was stirred in ether : iso-
hexane (1:1) overnight, the solvent removed by filtration to leave the title compound as a solid (0.186 g) which was isolated by decanting the solvent then drying the residue.

MS (APCI +ve) 357 (M-HCl+H)⁺

¹H NMR (DMSO-d₆) δ 9.20 (1H, s), 7.97 (3H, bs), 7.10 (1H, t), 6.94 (1H, d), 6.77 (1H, d),
4.05 (2H, t), 3.05-2.9 (2H, m), 2.1-2.0 (7H, m), 1.94 (3H, s), 1.75-1.55 (12H, m).

Example 3

N-(2-Chlorophenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide

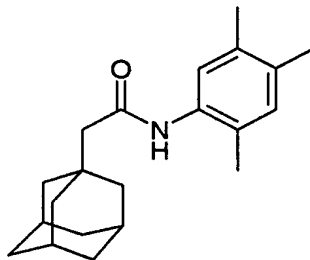


Prepared according to the method of Example 1b) from 1-adamantaneacetyl chloride (0.2 g) and 2-chlorolaniline (0.12 g) to give the title compound as a white solid (0.05 g).

Melting point: 122-124 °C

MS (APCI +ve) 304/306 (M+H)⁺

¹H NMR (CDCl₃) δ 8.40 (1H, d), 7.55 (1H, s), 7.40 (1H, dd), 7.3 (1H, m), 7.05 (1H, m),
2.16 (2H, s), 2.00 (3H, s), 1.75 (12H, m)

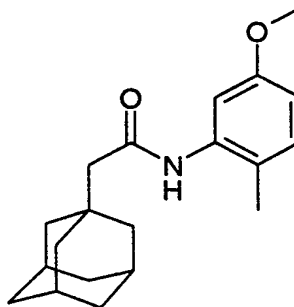
Example 4***N*-(2,4,5-Trimethylphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide**

Prepared according to the method of Example 1b) from 1-adamantaneacetyl chloride
5 (0.2 g) and 2,4,5-trimethylaniline (0.13 g) to give the title compound as a white solid
(0.042 g).

Melting point: 158 °C

MS (APCI +ve) 312 (M+H)⁺

10 ¹H NMR (DMSO-d₆) δ 9.00 (1H, s), 7.08 (1H, s), 6.94 (1H, s), 2.14 (6H, s), 2.10 (3H, s),
2.04 (2H, s), 1.98 (3H, s), 1.75 (12H, m)

Example 5***N*-(5-Methoxy-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide**

15

Prepared according to the method of Example 1b) from 1-adamantaneacetyl chloride
(0.2 g) and 5-methoxy-2-methylaniline (0.13 g) to give the title compound as a white solid
(0.043 g).

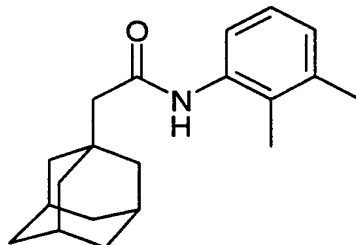
20 Melting point: 147 °C

MS (APCI +ve) 314 (M+H)⁺

¹H NMR (DMSO-d₆) 9.00 (1H, s), 7.07 (1H, d), 7.04 (1H, d), 6.65 (1H, dd), 3.69 (3H, s), 2.13 (3H, s), 2.09 (2H, s), 1.95 (3H, s), 1.75 (12H, m)

Example 6

5 *N*-(2,3-Dimethylphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide



Prepared according to the method of Example 1b) from 1-adamantaneacetyl chloride (0.2 g) and 2,3-dimethylaniline (0.11 g) to give the title compound as a white solid (0.034 g).

10

Melting point: 170 °C

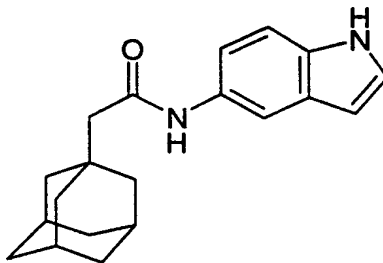
MS (APCI +ve) 298 (M+H)⁺

¹H NMR (DMSO-d₆) δ 9.20 (1H, s), 7.20-6.95 (3H, m), 2.23 (3H, s), 2.07 (5H, s), 1.95 (3H, s), 1.75 (12H, m)

15

Example 7

N-(5-Indolyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide



Prepared according to the method of Example 1b) from 1-adamantaneacetyl chloride (0.076 g) and 5-aminoindole (0.05 g) to give the title compound as a white solid (0.05 g).

20

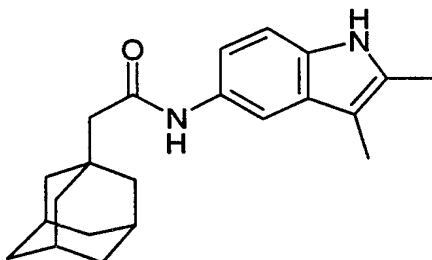
Melting point: 184-185 °C

MS (APCI +ve) 309 (M+H)⁺

¹H NMR (DMSO-d₆) δ 10.95 (1H, s), 9.51 (1H, s), 7.85 (1H, s), 7.28 (2H, m),
7.16 (1H, dd), 6.35 (1H, t), 2.04 (2H, s), 1.94 (3H, s), 1.70-1.50 (12H, m)

5 **Example 8**

***N*-(2,3-Dimethyl-5-indolyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide**



To a solution of 1-adamantaneacetic acid (0.30 g) in dichloromethane (10 ml) were added 4-dimethylaminopyridine (0.19 g) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.30 g). The reaction mixture was stirred for 0.5 hour before addition of 5-amino-2,3-dimethylindole (0.25 g). Stirring was then continued overnight at ambient temperature. The next day the reaction mixture was washed with dilute hydrochloric acid, water and brine, dried over sodium sulphate (Na₂SO₄) and finally concentrated under reduced pressure to leave a residue. Purification of the residue by silica gel chromatography, eluting with 40% ethyl acetate in *isohexanes*, gave the title compound as a white solid (0.14 g).

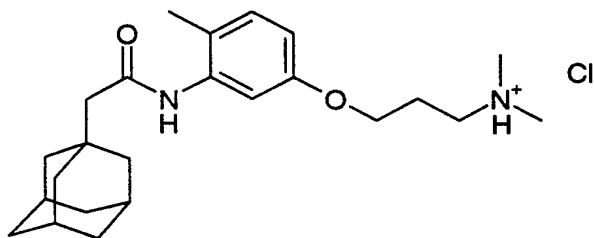
Melting point: 234-235 °C

MS (APCI +ve) 337 (M+H)⁺

¹H NMR (DMSO-d₆) δ 10.50 (1H, s), 9.46 (1H, s), 7.67 (1H, s), 7.08 (2H, m),
2.28 (3H, s), 2.03 (3H, s), 1.99 (2H, s), 1.94 (3H, s), 1.70-1.50 (12H, m)

Example 9

***N*-[5-(3-*N,N*-Dimethylaminopropoxy)-2-methylphenyl]-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide, hydrochloride**



5 To a solution of *N*-(5-methoxy-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide prepared as described in Example 5 (1.00 g) in dichloromethane (20 ml) was added borontribromide (4 ml of a 1.0M solution in dichloromethane) at -78 °C under an inert atmosphere. The reaction mixture was stirred for 24 hours and then warmed to ambient temperature and washed with brine. The organic layer was then dried over
10 magnesium sulphate (MgSO₄) and concentrated under reduced pressure to yield a residue. To a solution of the residue (200 mg) in *N,N*-dimethylformamide (10 ml) were added potassium carbonate (0.185 g) and *N,N*-dimethyl-3-chloropropylamine hydrochloride (0.11 g) and the reaction mixture was heated, with stirring, to 80 °C for 4 hours. Once
15 cooled, the reaction mixture was diluted with ethyl acetate and washed with saturated brine. The organic phase was separated, dried over magnesium sulphate (MgSO₄) and then passed through an "ISOLUTE" (trade mark) NH₂ solid phase extraction cartridge, eluting with ethyl acetate. Evaporation of the eluant, followed by treatment with 1.0M hydrogen chloride in ether and finally concentration under reduced pressure gave the title compound as a white solid (0.02 g).

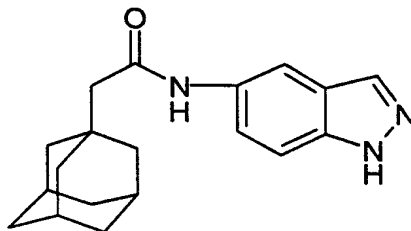
20

Melting point: 139-140 °C

MS (APCI +ve) 385 (M+H)⁺ (for free base)

¹H NMR (DMSO-d₆) δ 10.38 (1H, s), 9.05 (1H, s), 7.08 (2H, d+s), 3.95 (4H, m),
3.2 (2H, m), 2.78 (6H, 2s), 2.13 (3H, s), 2.10 (2H, s), 1.95 (3H, s), 1.6 (12H, m)

25

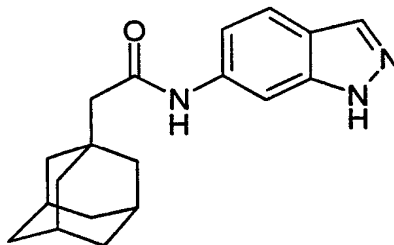
Example 10***N*-(5-Indazolyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide**

Prepared according to the method of Example 1b) from 1-adamantaneacetyl chloride
5 (0.1 g) and 5-aminoindazole (0.067 g) to give the title compound as a white solid (0.12 g).

Melting point: 265 °C

MS (APCI +ve) 310 (M+H)⁺

¹H NMR (DMSO-d₆) δ 12.93 (1H, s), 9.73 (1H, s), 8.12 (1H, s), 7.99 (1H, s),
10 7.40 (2H, m), 2.04 (2H, s), 1.94 (3H, s), 1.70-1.50 (12H, m)

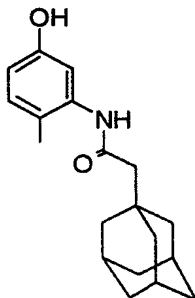
Example 11***N*-(6-Indazolyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide**

15 Prepared according to the method of Example 1b) from 1-adamantaneacetyl chloride
(0.2 g) and 6-aminoindazole (0.13 g) to give the title compound as a white solid (0.064 g).

Melting point: 245 °C

MS (APCI +ve) 310 (M+H)⁺

¹H NMR (DMSO-d₆) δ 12.84 (1H, s), 9.87 (1H, s), 8.16 (1H, s), 7.94 (1H, s),
20 7.62 (1H, d), 7.05 (1H dd), 2.04 (2H, s), 1.94 (3H, s), 1.70-1.50 (12H, m)

Example 12***N*-(5-Hydroxy-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide**

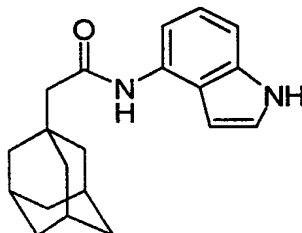
To a solution of *N*-(5-methoxy-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide
5 prepared as described in Example 5 (1.00 g) in dichloromethane (20 ml), was added boron
tribromide (4 ml of a 1.0M solution in dichloromethane) at -78 °C under an inert
atmosphere. The reaction mixture was stirred for 24 hours and then warmed to ambient
temperature and washed with brine. The organic layer was dried over magnesium sulphate
(MgSO₄) and concentrated under reduced pressure to yield a residue. Trituration with
10 diethyl ether gave a solid (0.335g). A portion of this material (0.050g) was further purified
by Supercritical Fluid chromatography using a Cyano column, eluting with a gradient of
methanol in supercritical carbon dioxide to give the title compound as a white solid.
(0.030g)

15 Melting point: 255-256 °C

MS (APCI +ve) 300 (M+H)⁺

¹H NMR (DMSO-d₆) δ 9.11 (1H, s), 8.92 (1H, s), 6.92 (1H, m), 6.45 (1H, dd),

2.04 (5H, s), 1.94 (3H, s), 1.70-1.50 (12H, m)

Example 13***N*-(1*H*-Indol-4-yl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide**

Prepared according to the method of Example 1b) from 1-adamantaneacetyl chloride
5 (0.074 g) and 4-aminoindole hydrochloride (0.059 g) to give the title compound as a white
solid (0.068 g).

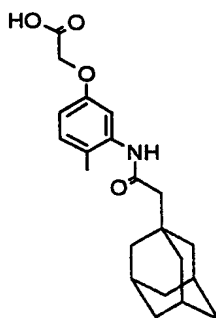
Melting point: 211-213 °C

MS (APCI +ve) 309 (M+H)⁺

10 ¹H NMR (DMSO-d₆) δ 11.07 (1H, s), 9.35 (1H, s), 7.53 (1H, d), 7.27 (1H, t), 7.12 (1H, d),
6.99 (1H, t), 6.66 (1H, s), 2.19 (2H, s), 1.94 (3H, s), 1.68 (6H, d), 1.68-1.58 (6H, m).

Example 14

15 **4-Methyl-3-[[1-oxo-2-(tricyclo[3.3.1.1^{3,7}]dec-1-yl)ethyl]amino]phenoxy-acetic acid,
hydrochloride salt**



To a solution of *N*-(5-Hydroxy-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide
from Example 12 (0.20 g) was added potassium carbonate (0.106g) and ethyl bromoacetate
(0.3ml). The reaction mixture was stirred and heated at 80°C for 24 hours. Once cooled,
20 the reaction mixture was diluted with ethyl acetate and washed with saturated brine. The
organic phase was separated, dried over magnesium sulphate (MgSO₄) and evaporated

under reduced pressure to leave a residue which was purified by silica gel chromatography eluting with iso-hexane/diethyl ether (1:1) to give a white solid. The solid was dissolved in dioxane (20ml) and the solution treated with 2M sodium hydroxide solution, the reaction mixture was stirred at ambient temperature for 24 hours, acidified (2M hydrochloric acid) and extracted into ethyl acetate. The organic phase was washed with brine, dried over magnesium sulphate (MgSO₄) and evaporated under reduced pressure. The residue was triturated with diethyl ether to leave the title compound as a white solid (0.070g).

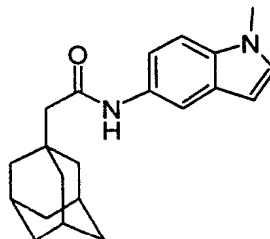
Melting point: 204-205 °C

MS (APCI +ve) 358 (M+H)⁺

¹H NMR (DMSO-d₆) δ 12.95 (1H, s), 9.03 (1H, s), 7.05 (2H, m), 6.60 (1H, dd), 4.58 (2H, s), 2.12 (3H, s), 2.090 (2H, s), 1.94 (3H, s), 1.70-1.50 (12H, m)

Example 15

N-(1-Methyl-1*H*-indol-5-yl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide



a) 1-Methyl-5-nitro-1*H*-indole

To a solution of 5-nitroindole (0.20 g) in tetrahydrofuran (2 ml) was added sodium hydride (0.06 g of 60% dispersion in oil) and evolution of gas noted. After stirring for 30 min methyl iodide (0.086 ml) was added to the dark brown reaction mixture and the reaction mixture heated to 65 °C for 2 hr before cooling to room temperature and partitioning between dichloromethane and water. Organic phase separated, washed with sodium thiosulphate solution, dried (Na₂SO₄) and concentrated to leave sub-title compound as a yellow solid (0.20 g).

¹H NMR (DMSO-d₆) δ 8.58 (1H, d), 8.04 (1H, dd), 7.65 (1H, d), 7.61 (1H, d), 6.75 (1H, dd), 3.88 (3H, s).

b) *N*-(1-Methyl-1*H*-indol-5-yl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide

5 To a solution of 1-methyl-5-nitroindole from step a) (0.11 g) in ethanol (10 ml) was added 10% palladium on carbon (0.023 g) and resulting suspension stirred under 4 bar pressure of hydrogen for 0.75 h before filtering off the catalyst and concentration at reduced pressure. The resulting residue was condensed with 1-adamantneacetyl chloride (0.10 g) according to the method of Example 1b) to give the title compound as a white
10 solid (0.11 g).

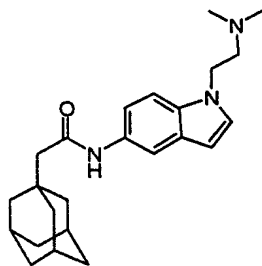
Melting point: 183-184 °C

MS (APCI +ve) 323 (M+H)⁺

¹H NMR (DMSO-d₆) δ 9.55 (1H, s), 7.87 (1H, d), 7.32 (1H, d), 7.26 (1H, d),
15 7.23 (1H, dd), 6.34 (1H, dd), 3.75 (3H, s), 2.04 (2H, s), 1.94 (3H, s), 1.75-1.50 (12H, m).

Example 16

***N*-(1-(*N,N*-Dimethylamino)ethyl-1*H*-indo-5-yl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide**



a) 1-(*N,N*-Dimethylamino)ethyl-5-nitro-1*H*-indole

20 Prepared according to the method of Example 15a) from 5-nitroindole (0.217 g) and dimethylaminoethyl chloride hydrochloride (0.21 g) to leave sub-title compound as an orange/brown solid (0.24 g).

¹H NMR (DMSO-d₆) δ 8.56 (1H, d), 8.02 (1H, dd), 7.71 (1H, d), 7.61 (1H, d),
25 6.74 (1H, dd), 4.35 (2H, t), 2.62 (2H, t), 2.17 (6H, s).

b) ***N*-(1-(*N,N*-Dimethylamino)ethyl-1*H*-indo-5-yl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide**

Prepared according to the method of Example 15b) from 1-(*N,N*-dimethylamino)ethyl-5-nitroindole (0.23 g) and 1-adamantaneacetyl chloride (0.21 g) to give the title compound as a white solid (0.22 g).

Melting point: 125-127 °C

MS (APCI +ve) 380 (M+H)⁺

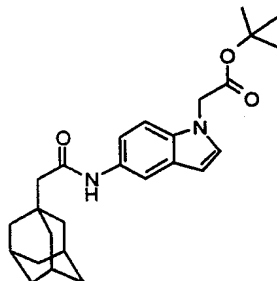
¹H NMR (DMSO-d₆) δ 9.54 (1H, s), 7.85 (1H, d), 7.36 (1H, d), 7.32 (1H, d),

7.20 (1H, dd), 6.33 (1H, d), 4.20 (2H, t), 2.58 (2H, t), 2.17 (6H, s), 2.04 (2H, s),

1.94 (3H, s), 1.65 (12H, m).

Example 17

5-[[1-Oxo-2-(tricyclo[3.3.1.1^{3,7}]dec-1-yl)ethyl]amino]-1*H*-indole-1-acetic acid, 1,1-dimethylethyl ester



a) **5-Nitro-1*H*-indole-1-acetic acid, 1,1-dimethylethyl ester**

Prepared according to the method of Example 15a) from 5-nitroindole (0.207 g) and 2-bromoacetic acid, 1,1-dimethylethyl ester (0.23 ml) to give sub-title compound as a yellow oily solid (0.29 g).

¹H NMR (DMSO-d₆) δ 8.58 (1H, d), 8.04 (1H, dd), 7.60 (2H, m), 6.77 (1H, dd),

3.15 (2H, s), 1.42 (9H, s)

b) 5-[[1-Oxo-2-(tricyclo[3.3.1.1^{3,7}]dec-1-yl)ethyl]amino]-1*H*-indole-1-acetic acid, 1,1-dimethylethyl ester

Prepared according to the method of Example 15b) from 5-nitro-1*H*-indole-1-acetic acid, 1,1-dimethylethyl ester (0.29 g) and 1-adamantaneacetyl chloride (0.20 g) to give the
5 title compound as a white solid (0.24 g).

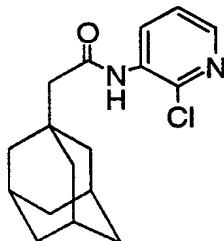
Melting point: 199 °C

MS (APCI +ve) 423 (M+H)⁺

¹H NMR (DMSO-d₆) δ 9.56 (1H, s), 7.86 (1H, d), 7.27 (1H, d), 7.22 (2H, m), 6.38 (1H, d),
10 4.94 (2H, s), 2.04 (2H, s), 1.94 (3H, s), 1.65 (12H, m), 1.41 (9H, s).

Example 18

***N*-(3-(2-Chloropyridyl))-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide**



15 Prepared according to the method of Example 1b) from 1-adamantaneacetyl chloride (0.5g) and 2-chloro-3-aminopyridine (0.31 g) to give the title compound as a white solid (0.27 g).

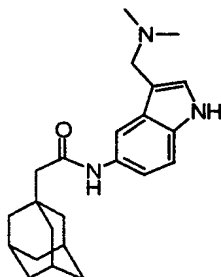
Melting point: 135-136 °C

20 MS (APCI +ve) 305 (M+H)⁺

¹H NMR (DMSO-d₆) δ 9.51 (1H, s), 8.22 (1H, dd), 8.15 (1H, dd), 7.4 (1H, dd),
2.20 (2H, s), 1.98 (3H, s), 1.60 (12H, m)

Example 19

***N*-(3-(*N,N*-Dimethylamino)methyl-1*H*-indo-5-yl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide**

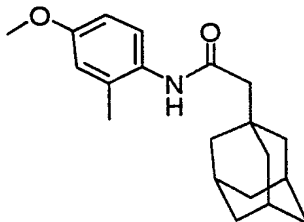


- 5 To a suspension of indole amide from Example 7 (0.163 g) in acetic acid (0.20 ml) was added aqueous dimethylamine (0.065 ml of a 40% solution), aqueous formaldehyde (0.043 ml of a 37% solution) and acetic acid (0.10 ml) and resulting reaction mixture heated to 60 °C for 2 hr before cooling to 0-5 °C. Reaction mixture made alkaline by addition of aqueous ammonia solution and partitioned between ethyl acetate and water.
- 10 Organic phase separated, washed with brine, dried (Na₂SO₄) and concentrated and residue purified by chromatography on Al₂O₃ eluting with 0-10% methanol in dichloromethane to give the title compound as a brown solid (0.07 g).

Melting point: 194-213 °C (dec.)

- 15 MS (APCI +ve) 366 (M+H)⁺

¹H NMR (DMSO-d₆) δ 11.24 (1H, s), 9.62 (1H, s), 8.00 (1H, s), 7.46 (1H, d), 7.32 (1H, d), 7.21 (1H, dd), 4.12 (2H, br s), 2.55 (6H, s), 2.06 (2H, s), 1.94 (3H, s), 1.70-1.58 (12H, m).

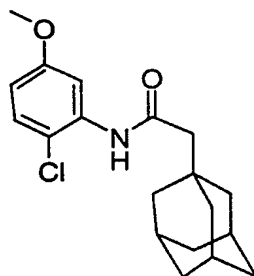
Example 20***N*-(4-Methoxy-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide**

Prepared according to the method of Example 1b) from 1-adamantaneacetyl chloride
5 (2.0g) and 4-methoxy-2-methylaniline (1.29 g) to give the title compound as a white solid
(1.37 g).

Melting point: 156-157 °C

MS (APCI +ve) 314 (M+H)⁺

10 ¹H NMR (DMSO-d₆) δ 9.01 (1H, s), 7.15 (1H, d), 6.80 (1H, d), 6.7 (1H, dd), 3.7 (3H, s),
2.20 (3H, s), 2.05 (2H, s), 1.95 (3H, s), 1.60 (12H, m)

Example 21***N*-(2-Chloro-5-methoxyphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide**

15

Prepared according to the method of Example 1b) from 1-adamantaneacetyl chloride
(2.0g) and 2-chloro-5-methoxyaniline (1.49 g) to give the title compound as a white solid
(0.60 g).

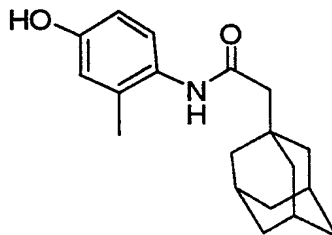
20 Melting point: 122-123 °C

MS (APCI +ve) 334 (M+H)⁺

¹H NMR (DMSO-d₆) δ 9.20 (1H, s), 7.36 (2H, m), 6.76 (1H, dd), 6.7 (1H, dd), 3.73 (3H, s), 2.20 (2H, s), 1.95 (3H, s), 1.60 (12H, m)

Example 22

5 ***N*-(4-Hydroxy-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide**



To a solution of *N*-(4-Methoxy-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide from Example 20 (1.20 g) in dichloromethane (50 ml) at -78 °C was added boron tribromide (4 ml of a 1.0M solution in dichloromethane) under an inert atmosphere. The reaction mixture was stirred for 24 hours and then warmed to ambient temperature and washed with brine. The organic layer was then dried over magnesium sulphate (MgSO₄) and concentrated under reduced pressure to yield a residue which was purified by silica gel chromatography eluting with iso-hexane/diethyl ether (1:1) to give the title compound as a white solid. (0.54g)

15

Melting point: 205-206 °C

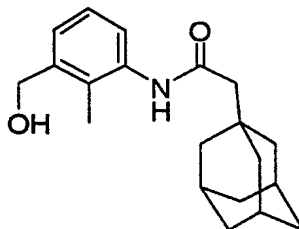
MS (APCI +ve) 300 (M+H)⁺

¹H NMR (DMSO-d₆) δ 9.15 (1H, s), 8.91 (1H, s), 7.00 (1H, d), 6.54 (2H, m), 2.53 (3H, s), 2.03 (2H, s), 1.94 (3H, s), 1.70-1.50 (12H, m)

20

Example 23

N-(3-Hydroxymethyl-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide



Prepared according to the method of Example 1b) from 1-adamantaneacetyl chloride
(2.0g) and 3-amino-2-methylbenzyl alcohol (1.29 g). Silica gel chromatography, eluting
with 5% ethylacetate in dichloromethane gave the title compound as a white solid (0.80 g).

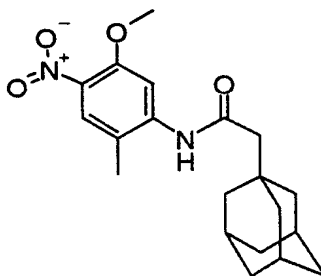
Melting point: 205-206 °C

MS (APCI +ve) 314 (M+H)⁺

¹H NMR (DMSO-d₆) δ 9.16 (1H, s), 7.20-7.05 (3H, m), 5.07 (1H, bs), 4.47 (2H, s),
2.09 (2H, s), 2.08 (3H,s), 1.95 (3H, s), 1.60 (12H, m)

Example 24

N-(5-Methoxy-2-methyl-3-nitrophenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide



Prepared according to the method of Example 1b) from 1-adamantaneacetyl chloride
(2.0g) and 5-methoxy-2-methyl-4-nitroaniline (1.71 g). Silica gel chromatography, eluting
with iso-hexane/diethyl ether (1:1), gave the title compound as a yellow solid (1.10 g).

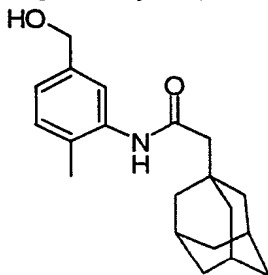
Melting point: 141-142 °C

MS (APCI +ve) 359 (M+H)⁺

¹H NMR (DMSO-d₆) δ 9.26 (1H, s), 7.82 (1H, s), 7.76 (1H, s), 3.86 (3H, s), 2.23 (3H, s), 2.08 (2H,s), 1.95 (3H, s), 1.60 (12H, m)

Example 25

5 *N*-(5-Hydroxymethyl-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide



Prepared according to the method of Example 1b) from 1-adamantaneacetyl chloride (2.0g) and 3-amino-4-methylbenzyl alcohol (1.29 g). Silica gel chromatography, eluting with 5% ethylacetate in dichloromethane gave the title compound as a white solid (1.10 g).

10

Melting point: 190 °C

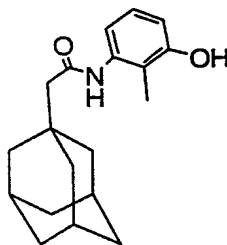
MS (APCI +ve) 314 (M+H)⁺

¹H NMR (DMSO-d₆) δ 8.54 (1H, bs), 7.46 (1H, s), 7.1 (2H, m), 4.70 (1H, bs), 4.54 (2H, d), 2.24 (3H, s), 2.15 (2H,s), 2.0 (3H, s), 1.70 (12H, m)

15

Example 26

N-(3-Hydroxy-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide



Prepared according to the method of Example 1b) from 1-adamantaneacetyl chloride (0.81) and 3-amino-2-methylphenol (0.5 g) to give the title compound as a white solid (0.5 g).

20

Melting point: 211 °C

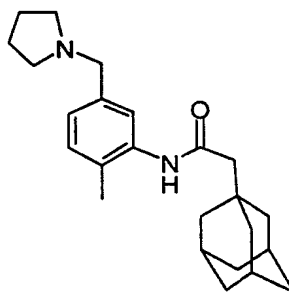
MS (APCI +ve) 300 (M+H)⁺

¹H NMR (DMSO- d₆) δ 9.28 (1H, bs), 9.04 (1H, bs), 6.91 (1H, t), 6.8 (1H, d), 6.6 (1H, d), 2.05 (2H, s), 1.98 (3H, s), 1.94 (3H, bs), 1.6 (12H, m)

5

Example 27

***N*-(2-Methyl-5-(1-pyrrolidinemethyl)phenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide, hydrochloride**



10 To a solution of *N*-(5-Hydroxymethyl-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide from Example 25) (1.0 g) in acetonitrile was added triphenylphosphine (0.93g) and carbon tetrabromide (1.2g). The reaction mixture was stirred at ambient temperature for 24 hours and evaporated under reduced pressure. The residue was purified by silica gel chromatography eluting with iso-hexane/diethyl ether to give a white solid. A portion
15 (0.1g) of the solid was dissolved in acetonitrile (3ml) and treated with pyrrolidine (0.2ml). The reaction mixture was stirred and heated at 80°C for 24 hours. Once cooled, the reaction mixture was diluted with ethyl acetate and washed with saturated brine. The organic phase was separated, dried over magnesium sulphate (MgSO₄), treated with a solution of hydrogen chloride in diethyl ether (1ml of 1.0M) and evaporated under
20 reduced pressure to leave a residue which was triturated with iso-hexane to give the title compound as an off-white solid. (0.030g)

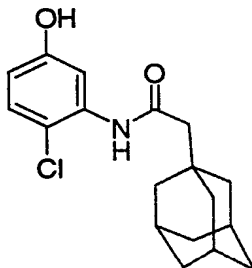
Melting point: 214-215 °C

MS (APCI +ve) 367 (M+H)⁺ for free base.

^1H NMR (DMSO- d_6) δ 9.22 (1H, s), 7.60 (1H, s), 7.27(2H, s), 4.27 (2H, d), 3.35 (2H, m), 3.05 (2H, m), 2.21 (3H,s), 2.1 (2H, s), 2.0-1.8 (7H, m), 1.60 (12H, m)

Example 28

5 *N*-(2-Chloro-5-hydroxyphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide



Prepared according to the method of Example 1b) from 1-adamantaneacetyl chloride (2.9g) and 2-chloro-4-hydroxyaniline (2.0 g). Silica gel chromatography, eluting with 30% diethyl ether in iso-hexane, followed by recrystallisation from acetonitrile gave the title
10 compound as a white solid (0.15 g).

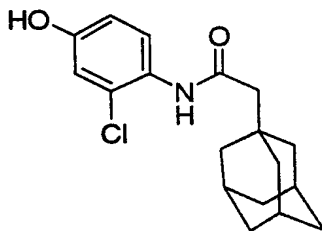
Melting point: 224-225 °C

MS (APCI +ve) 320 (M+H)⁺

^1H NMR (DMSO- d_6) δ 9.76(1H, s), 9.14 (1H, s), 7.26 (1H, d), 6.83 (1H, d), 6.69 (1H, dd),
15 2.05 (2H, s), 1.95 (3H, s), 1.60 (12H, m)

Example 29

N-(2-Chloro-4-hydroxyphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide



20 Prepared according to the method of Example 1b) from 1-adamantaneacetyl chloride (2.9 g) and 2-chloro-4-hydroxyaniline to give the title compound as a white solid. (0.15g).

Melting point: 224-225 °C

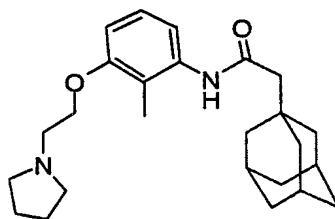
MS (APCI +ve) 320 (M+H)⁺

¹H NMR (DMSO-d₆) δ 9.65 (1H, s), 9.09 (1H, s), 7.23 (2H, m), 6.55 (1H, dd), 2.20 (2H, s), 1.95 (3H, s), 1.60 (12H, m)

5

Example 30

***N*-(2-Methyl-3-(2-(1-pyrrolidino)ethoxy)phenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide, hydrochloride**

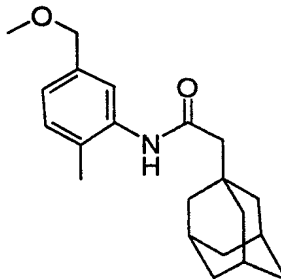


10 To a solution of *N*-(3-Hydroxy-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide from Example 26 (0.060g), in acetonitrile (3ml), was added caesium carbonate (0.196g) and *N*-(2-chloroethyl)-pyrrolidine hydrochloride (0.068g). The reaction mixture was stirred and heated at 80°C for 24 hours. After cooling, the reaction mixture was diluted with ethyl acetate and washed with water. The organic phase was dried over magnesium
15 sulphate and evaporated under reduced pressure to leave a residue which was purified by Supercritical Fluid Chromatography using a gradient elution of 0.1% v/v solution of diethylamine in methanol and supercritical carbon dioxide on a Cyano column. The pure product was dissolved in dichloromethane, treated with 1.0M solution of hydrogen chloride in diethyl ether and evaporated under reduced pressure to leave the title compound as a
20 white solid. (0.010g)

Melting point: 105-106 °C

MS (APCI +ve) 397 (M+H)⁺ for free base.

¹H NMR (DMSO-d₆) δ 9.22 (1H, s), 7.12 (1H, t), 6.97 (1H, d), 6.81 (1H, d), 4.30 (2H, t),
25 3.60 (4H, m), 3.10 (2H, m), 2.05 (6H, s), 1.95 (6H, m), 1.60 (12H, m)

Example 31***N*-(5-Methoxymethyl-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide**

To a solution of the benzyl bromide prepared in Example 27 (0.10 g) in methanol (5ml) and added sodium methoxide (0.020g). The reaction mixture was stirred at ambient temperature for 2 hours then evaporated under reduced pressure to leave a residue which was dissolved in ethyl acetate and washed with 2M hydrochloric acid. The organic phase was dried over magnesium sulphate and evaporated under reduced pressure, the residue was triturated with diethyl ether to yield the title compound as a white solid. (0.015g)

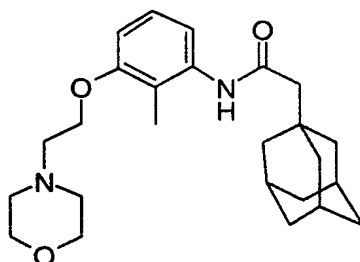
Melting point: 127-128 °C

MS (APCI +ve) 328 (M+H)⁺

¹H NMR (DMSO-d₆) δ 9.10 (1H, s), 7.33 (1H, s), 7.15 (1H, d), 6.99 (1H, d), 4.34 (2H, s), 2.20 (3H, s), 2.10 (2H, s), 1.95 (6H, m), 1.60 (12H, m)

Example 32

***N*-(2-Methyl-3-(2-(1-morpholino)ethyloxy)phenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide, hydrochloride**



- 5 Prepared according to the method of Example 30 from *N*-(3-Hydroxy-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide (0.060g) and *N*-(2-chloroethyl)-morpholine hydrochloride (0.075g) to give the title compound as a white solid. (0.024g).

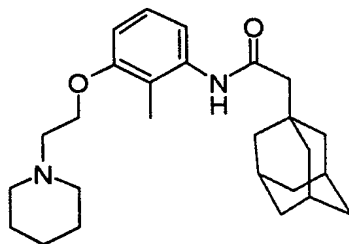
Melting point: 195-197 °C

- 10 MS (APCI +ve) 413 (M+H)⁺ for free base.

¹H NMR (DMSO-d₆) δ 11.36 (1H, bs), 9.23 (1H, s), 7.15 (1H, t), 6.99 (1H, d), 6.83 (1H, d), 4.42 (2H, t), 4.10-3.0 (12H, m), 2.08 (2H, s), 2.07 (3H, s), 1.95 (3H, s), 1.60 (12H, m)

15 **Example 33**

***N*-(2-Methyl-3-(2-(1-piperidino)ethyloxy)phenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide, hydrochloride**



- 20 Prepared according to the method of Example 30 from *N*-(3-Hydroxy-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide (0.060g) and *N*-(2-chloroethyl)-piperidine hydrochloride (0.074g) to give the title compound as a white solid (0.036g).

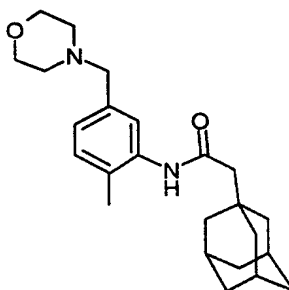
Melting point: 105-106 °C

MS (APCI +ve) 412(M+H)⁺ for free base.

¹H NMR (DMSO-d₆) δ 10.62 (1H, bs), 9.24 (1H, s), 7.12 (1H, t), 6.97 (1H, d),
6.82 (1H, d), 4.42 (2H, t), 3.50 (4H, m), 3.05 (2H, m), 2.10 (2H, s), 2.05 (3H, s),
2.0 (3H, s), 1.90-1.50 (18H, m)

Example 34

N-(2-Methyl-5-(1-morpholinomethyl)phenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
hydrochloride



Prepared according to the method of Example 27 from *N*-(5-Hydroxymethyl-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide and morpholine hydrochloride (0.040ml). Purification by Supercritical Fluid chromatography using a gradient elution of 0.1% v/v solution of diethylamine in methanol and supercritical carbon dioxide on a
Cyano column gave the pure product which was dissolved in dichloromethane, treated with
1.0M solution of hydrogen chloride in diethyl ether and evaporated under reduced pressure
to leave the title compound as a white solid (0.085g).

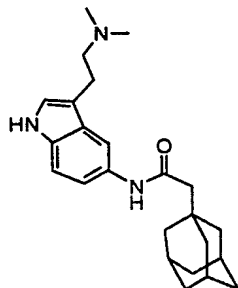
Melting point: 204-205 °C

MS (APCI +ve) 384(M+H)⁺ for free base.

¹H NMR (DMSO-d₆) δ 9.22 (1H, s), 7.60 (1H, s), 7.27 (2H, s), 4.30 (2H, d), 4.0 (2H, m),
3.8-3.6 (4H, m), 3.40-2.8 (7H, m), 2.25 (3H, s), 2.15 (2H, s), 2.0 (3H, s), 1.60 (12H, m)

Example 35

***N*-(5-(3-(2-*N,N*-dimethylaminoethyl)indolyl))-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide, hydrochloride**



- 5 Prepared according to the method of Example 1b) from 1-adamantaneacetyl chloride (0.040g) and 5-amino-3-(2-dimethylaminoethyl)indole dihydrochloride (0.18 g). Supercritical Fluid chromatography using a gradient elution of 0.1% v/v solution of diethylamine in methanol and supercritical carbon dioxide on a Cyano column gave the pure product which was dissolved in dichloromethane, treated with 1.0M solution of
- 10 hydrogen chloride in diethyl ether and evaporated under reduced pressure to leave the title compound as a pale yellow solid. (0.031g).

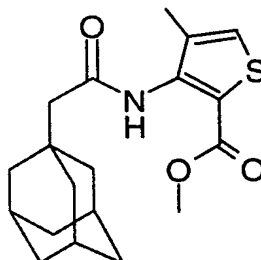
Melting point: 145-147 °C

MS (APCI +ve) 380 (M+H)⁺ for free base

- 15 ¹H NMR (DMSO-d₆) δ 10.89 (1H, s), 9.58 (1H, s), 7.95 (1H, d), 7.25 (1H, dd), 7.15 (1H, d), 7.12 (1H, dd), 3.33 (2H, m), 3.05 (2H, m), 2.85 (6H, 2s), 2.03 (2H, s), 1.95 (3H, s), 1.60 (12H, m)

Example 36

Methyl 4-methyl-3-[[1-oxo-2-(tricyclo[3.3.1.1^{3,7}]dec-1-yl)ethyl]amino]thiophene-2-carboxylate

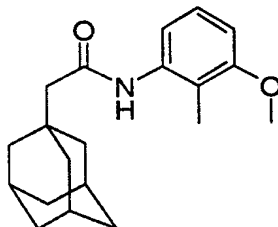


5 A solution of 1-adamantaneacetyl chloride (0.2 g) prepared as described in Example 1a) was added to a solution of methyl 3-amino-4-methylthiophene-2-carboxylate (0.16 g) in pyridine (2 ml) and dichloromethane (4 ml). The reaction mixture was stirred at ambient temperature for 2 days before being diluted with ethyl acetate. The organic phase was then washed with dilute hydrochloric acid and water, dried over magnesium sulphate (MgSO₄) and finally concentrated under reduced pressure to give an oil. Purification of the residue
10 by silica gel chromatography, eluting with 10% ethyl acetate in *iso*hexanes, gave the title compound as a white solid (0.049 g).

Melting point: 124-124.5 °C

15 MS (APCI +ve) 348 (M+H)⁺

¹H NMR (CDCl₃) δ 8.76 (1H, s), 7.13 (1H, s), 3.86 (3H, s), 2.23 (3H, s), 2.18 (2H, s), 2.0 (3H, bs), 1.70 (12H, m).

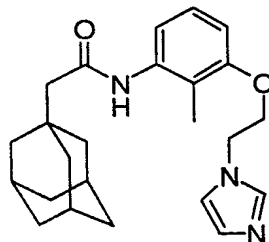
Example 37***N*-(3-Methoxy-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide**

Diethyl azodicarboxylate (0.20 ml) was added to a solution of *N*-(3-hydroxy-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide (0.20 g, Example 26), methanol (0.10 ml) and triphenylphosphine (0.41 g) in toluene (10 ml) and tetrahydrofuran (5 ml). After 2 hours stirring at room temperature further triphenylphosphine (0.20 g) and diethyl azodicarboxylate (0.10 ml) were added and the solution stirred for 2 hours. The reaction mixture was concentrated under reduced pressure and the residue purified by silica gel chromatography eluting with dichloromethane : ethyl acetate (19:1) to give the title compound as a colourless solid (0.20 g).

Melting point: 173-175 °C

MS (APCI +ve) 314 (M+H)⁺

¹H NMR (CDCl₃) δ 7.48 (1H, d), 7.16 (1H, t), 6.86 (1H, bs), 6.69 (1H, d), 3.82 (3H, s), 2.13 (5H, s), 2.00 (3H, s), 1.75-1.6 (12H, m).

Example 38***N*-(2-Methyl-3-(2-(1-imidazolo)ethyloxy)phenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide**

20

Diethyl azodicarboxylate (0.060 ml) was added to a solution of *N*-(3-hydroxy-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide (0.100 g, Example 26), 1-(2-

hydroxyethyl)imidazole (0.048 g, *J. Heterocyclic Chem.*, 1990, **27**, 215) and triphenylphosphine (0.097 g) in tetrahydrofuran (4 ml). After 24 hours stirring at room temperature further triphenylphosphine (0.100 g) and diethyl azodicarboxylate (0.060 ml) were added and the solution stirred for 6 days. The reaction mixture was concentrated under reduced pressure and the residue purified by NPHPLC on a Novapak® column using a Gilson automated chromatography machine eluting with 0-10% ethanol in dichloromethane to give an oil which was triturated with ether to give the title compound as a colourless solid (0.041 g).

10 Melting point: 119.5-121 °C

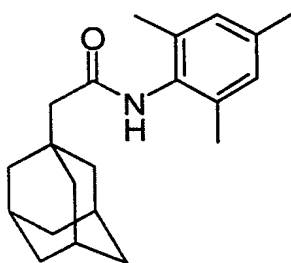
MS (APCI +ve) 394 (M+H)⁺

¹H NMR (CDCl₃) δ 7.60 (1H, s), 7.51 (1H, d), 7.14 (1H, t), 7.08 (1H, s), 7.03 (1H, s), 6.85 (1H, bs), 6.61 (1H, d), 4.37 (2H, t), 4.21 (2H, t), 2.13 (2H, s), 2.09 (3H, s), 2.00 (3H, s), 1-8-1.6 (12H, m).

15

Example 39

N-(2,4,6-Trimethylphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide



Thionyl chloride (3 ml) was added to 1-adamantaneacetic acid (0.50 g) and the reaction heated at reflux for 2 minutes. The excess thionyl chloride was removed by concentration under reduced pressure and the residue was dissolved in dichloromethane (5 ml). This solution was added to a solution of 2,4,6-trimethylaniline (0.72 ml) in dichloromethane (20 ml) and triethylamine (1 ml) at room temperature over 1 minute. After 5 minutes the reaction mixture was concentrated under reduced pressure and the residue added to a column of silica. The mixture was then chromatographed eluting with

20

25

dichloromethane then dichloromethane : ethyl acetate (9:1) to give the title compound as a colourless solid (0.469 g).

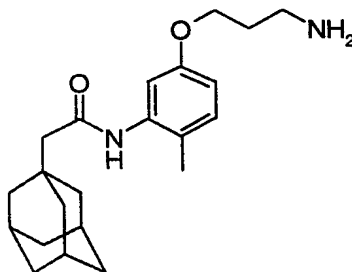
Melting point: 212-215 °C

5 MS (APCI +ve) 312 (M+H)⁺

¹H NMR (DMSO-d₆) δ 8.97 (1H, s), 6.85 (2H, s), 2.21 (3H, s), 2.10 (6H, s), 2.06 (2H, s), 1.95 (3H, s), 1.8-1.5 (12H, m).

Example 40

10 ***N*-(5-(3-Aminopropoxy)-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide, hydrochloride**



Prepared according to the method of Example 2 using diethyl azodicarboxylate (1.05 ml), *N*-(5-hydroxy-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide (0.506 g, Example 12), tert-butyl *N*-(3-hydroxypropyl)carbamate (1.15 g) and triphenylphosphine (1.75 g) to give the title compound as a yellow solid (0.21 g).

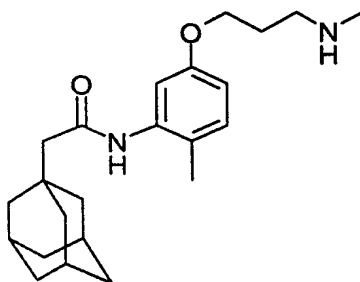
Melting point: 145 °C (dec.)

MS (APCI +ve) 357 (M-HCl+H)⁺

20 ¹H NMR (DMSO-d₆) δ 9.05 (1H, s), 7.91 (3H, bs), 7.15-7.05 (2H, m), 6.66 (1H, dd), 3.99 (2H, t), 2.94 (2H, t), 2.13 (3H, s), 2.10 (2H, s), 2.05-1.9 (5H, m), 1.75-1.55 (12H, m).

Example 41

***N*-(5-(3-(*N*-Methylamino)propyloxy)-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide, hydrochloride**



5 Diethyl azodicarboxylate (0.50 ml) was added to a solution of *N*-(5-hydroxy-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide (0.50 g, Example 12), tert-butyl *N*-(3-hydroxypropyl)-*N*-methylcarbamate (0.60 g, J. Org. Chem., 1988, 53(10), 2229) and triphenylphosphine (0.88 g) in tetrahydrofuran (5 ml). After stirring for 19 hours at room temperature further triphenylphosphine (0.90 g) and diethyl azodicarboxylate (0.50 ml) were added. After stirring for 4 hours at room temperature further triphenylphosphine (0.90 g) and diethyl azodicarboxylate (0.50 ml) were added and the reaction mixture was stirred for 3 days. The reaction was then concentrated under reduced pressure and the residue was purified by silica gel chromatography eluting with dichloromethane : ethyl acetate (9:1) to give material that was further purified by chromatography over a
15 Dynamax® column using a Gilson automated chromatography machine eluting with iso-hexane : ethyl acetate (4:1) to give the Mitsunobu reaction product (0.29 g) which was dissolved in methanol (10 ml). A solution of hydrogen chloride (generated by slow addition of acetyl chloride (12 ml) to methanol (10 ml) at 0°C **CARE - Very Exothermic**) was then added to the latter solution and the reaction stirred at room temperature for 1
20 hour. The reaction was then concentrated under reduced pressure to give the title compound as a yellow solid (0.13 g).

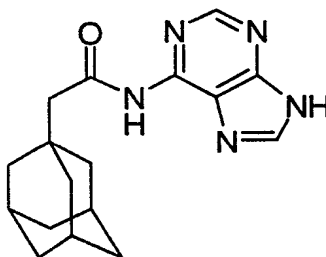
MS (APCI +ve) 371 (M-HCl+H)⁺

¹H NMR (DMSO-d₆) δ 9.05 (1H, s), 8.76 (2H, bs), 7.15-7.05 (2H, m), 6.66 (1H, dd), 3.99 (2H, t), 3.1-2.95 (2H, m), 2.6-2.5 (3H, m), 2.13 (3H, s), 2.10 (2H, s), 2.1-2.0 (2H, m), 1.94 (3H, m), 1.75-1.55 (12H, m).

5

Example 42

N6-(Tricyclo[3.3.1.1^{3,7}]decane-1-acetyl)adenine



To a solution of 1-adamantaneacetyl chloride from Example 1a) (0.226 g) in
10 dichloromethane (5 ml) was added 4-nitrophenol (0.149 g) and reaction mixture stirred at room temperature for 1 hr before concentration at reduced pressure. The resulting 4-nitrophenol ester was used without further purification.

To a suspension of the 4-nitrophenol ester (0.209 g), adenine (0.09 g) in
dimethylsulphoxide (1.4 ml) was added triethylamine (0.19 ml) and reaction mixture
15 heated to 90 °C for 2 days before cooling to room temperature. Reaction mixture was poured into aqueous sodium hydrogencarbonate solution and extracted with ethyl acetate. Organic extracts combined, washed with water (x 3), brine, dried (Na₂SO₄) and concentrated at reduced pressure. Trituration of the residue with isohexane and ether left the product as a pale yellow solid (0.036 g).

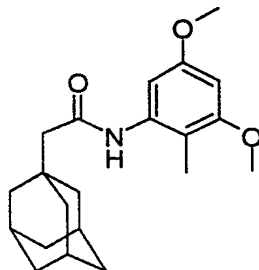
20

Melting point: 309 °C (dec.)

MS (APCI +ve) 312 (M+H)⁺

¹H NMR (DMSO-d₆) δ 12.10 (1H, s), 11.06 (1H, s), 8.61 (1H, s), 8.40 (1H, s), 2.29 (2H, s), 1.92 (3H, s), 1.66 (6H, d), 1.60 (6H, m).

25

Example 43***N*-(3,5-Dimethoxy-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide****a) 3,5-Dimethoxy-2-methylbenzoic acid**

5 To a solution of methyl 3,5-dimethoxy-2-methylbenzoate (5.83 g, *J.C.S. Perkin I*, 1973, 2853.) in methanol (80 ml) was added a solution of aqueous sodium hydroxide (10%, 80 ml) and reaction mixture stirred at room temperature for 1 hour. The reaction was then concentrated under reduced pressure to approximately half of the original volume before adding aqueous hydrochloric acid (200 ml). The white precipitate that formed was
 10 extracted with ethyl acetate (2 x 250 ml). The combined extracts were dried over anhydrous magnesium sulphate, filtered and concentrated under reduced pressure to give the sub-title compound as a colourless solid (5.41 g).

¹H NMR (CDCl₃) δ 7.10 (1H, d), 6.64 (1H, d), 3.84 (6H, s), 2.45 (3H, s).

b) *N*-(3,5-Dimethoxy-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide

Triethylamine (0.8 ml) followed by diphenylphosphoryl azide (1.2 ml) were added to a solution of 3,5-dimethoxy-2-methylbenzoic acid (1.0 g) in tert-butanol (30 ml) and the mixture was heated at reflux temperature for 12 hours. The reaction was cooled and
 20 concentrated under reduced pressure. The residue was partitioned between aqueous sodium hydroxide (2M, 100 ml) and dichloromethane (300 ml). The organic phase was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to give an oil (0.74 g) which was dissolved in methanol (10 ml). A solution of hydrogen chloride (generated by slow addition of acetyl chloride (12 ml) to methanol (10 ml) at 0°C
 25 **CARE - Very Exothermic**) was then added to the latter solution and the reaction stirred at

room temperature for 1 hour. The reaction was concentrated under reduced pressure and the residue partitioned between an aqueous solution of saturated sodium hydrogen carbonate (100 ml) and dichloromethane (100 ml). The organic phase was dried over magnesium sulphate, filtered and concentrated under reduced pressure to give an oil (0.5 g) which was dissolved in dichloromethane (10 ml) and triethylamine (2 ml). A solution of 1-adamantaneacetyl chloride (generated from 1-adamantaneacetic acid (0.50 g) and thionyl chloride) in dichloromethane (5 ml) was added to the latter solution and the mixture stirred at room temperature for 2 hours. The reaction was diluted with dichloromethane (100 ml) and the solution washed with aqueous hydrochloric acid (2M, 50 ml) then an aqueous solution of saturated sodium hydrogen carbonate (50 ml). The organic phase was dried over anhydrous magnesium sulphate, filtered and concentrated under reduced pressure. The residue was purified by column chromatography over silica eluting with dichloromethane then dichloromethane : ethyl acetate (19:1) to give the title compound as a colourless solid (0.54 g).

15

Melting point: 201-203 °C

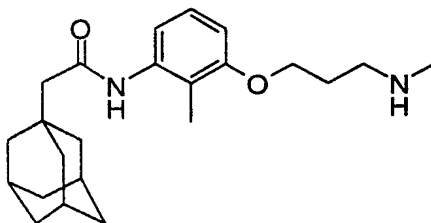
MS (APCI +ve) 344 (M+H)⁺

¹H NMR (DMSO-d₆) δ 9.08 (1H, s), 6.61 (1H, d), 6.38 (1H, d), 3.76 (3H, s), 3.70 (3H, t), 2.07 (2H, s), 1.94 (6H, s), 1.75-1.55 (12H, m).

20

Example 44

***N*-(3-(3-(*N*-Methylamino)propoxy)-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide, hydrochloride**



25

Dry dichloromethane (40 ml), triphenylphosphine (3.28 g), imidazole (1.05 g) and iodine (3.85 g) were combined in that order. A solution of tert-butyl *N*-(3-hydroxypropyl)-

N-methylcarbamate (1.90 g, J. Org. Chem., 1988, 53(10), 2229) in dichloromethane (10 ml) was added and the resulting reaction mixture stirred at room temperature for 1 hour. An aqueous solution of sodium hydrogen sulphite (6 g in 100 ml of water) was then added and the organic layer separated. The latter was dried over anhydrous magnesium sulphate, filtered and concentrated under reduced pressure. The residue was purified by column chromatography over silica eluting with iso-hexane : ether (7:3) to give tert-butyl *N*-(3-iodopropyl)-*N*-methylcarbamate (2.54 g) which was used immediately.

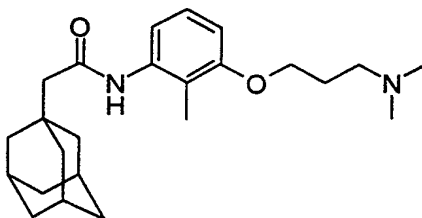
Caesium carbonate (0.655 g) was added to a suspension of *N*-(3-hydroxy-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide (0.453 g, Example 26) in acetonitrile (35 ml) and the mixture heated at 100°C for 10 minutes. After cooling to room temperature a solution of tert-butyl *N*-(3-iodopropyl)-*N*-methylcarbamate (0.600 g) in acetonitrile (5 ml) was added and the reaction heated at reflux for 90 minutes. The reaction was concentrated under reduced pressure and the residue partitioned between dichloromethane (100 ml) and water (100 ml). The organic layer was dried over anhydrous magnesium sulphate, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with dichloromethane : ethyl acetate (9:1) to give a solid that was dissolved in methanol (10 ml). A solution of hydrogen chloride (generated by slow addition of acetyl chloride (12 ml) to methanol (15 ml) at 0°C **CARE - Very Exothermic**) was then added to the latter solution and the reaction stirred at room temperature for 1 hour. The reaction was concentrated under reduced pressure to give a gum that was scratched under ether : hexane (1:1) (20 ml) to give the title compound as a pale yellow powder (0.477 g).

MS (APCI +ve) 371 (M-HCl+H)⁺

¹H NMR (DMSO-d₆) δ 9.20 (1H, s), 8.82 (2H, bs), 7.10 (1H, t), 6.94 (1H, d), 6.78 (1H, d), 4.05 (2H, t), 3.15-3.0 (2H, m), 2.58 (3H, t), 2.15-2.0 (7H, m), 1.94 (3H, m), 1.75-1.55 (12H, m).

Example 45

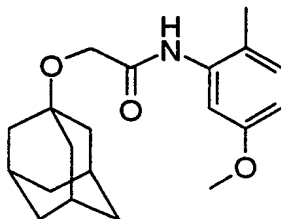
***N*-(5-(3-(*N,N*-Dimethylamino)propyloxy)-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide, hydrochloride**



5 Caesium carbonate (1.31 g) was added to a suspension of *N*-(3-hydroxy-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide (0.473 g, Example 26) in acetonitrile (35 ml) and the mixture heated at 80°C for 5 minutes. After cooling to room temperature solid *N,N*-dimethyl-3-chloropropylamine (0.274 g) was added and the reaction heated at reflux overnight. The reaction was concentrated under reduced pressure and the residue
10 partitioned between dichloromethane (100 ml) and water (100 ml). The organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. The residue was purified by column chromatography over silica eluting with dichloromethane : ethanol : triethylamine (95:4:1) to give a yellow gum. This was dissolved in methanol (10 ml) and treated with an excess of ethereal hydrogen chloride
15 (1M, 5 equivalents). The solution was concentrated under reduced pressure to give a gum that was stirred for 2 days in ether (20 ml) to give a solid which was isolated by filtration (0.588 g).

MS (APCI +ve) 385 (M-HCl+H)⁺

20 ¹H NMR (DMSO-d₆) δ 10.33 (1H, bs), 9.21 (1H, s), 7.10 (1H, t), 6.94 (1H, d), 6.78 (1H, d), 4.04 (2H, t), 3.3-3.1 (2H, m), 2.79 (6H, d), 2.2-2.1 (2H, m), 2.08 (2H, s), 2.05 (3H, s), 1.95 (3H, s), 1.75-1.55 (12H, m).

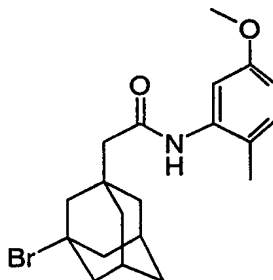
Example 46***N*-(5-Methoxy-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decanyloxy-1-acetamide**

Thionyl chloride (3 ml) was added to 1-adamantyloxyacetic acid (0.38 g, CA 1966, 65,
2149a) and the reaction heated at reflux for 2 minutes. The excess thionyl chloride was
5 removed by concentration under reduced pressure and the residue was then dissolved in
dichloromethane (2.5 ml). This solution was then added over 1 minute to a solution of 5-
methoxy-2-methylaniline (0.37 g) in dichloromethane (20 ml) and triethylamine (1 ml) at
room temperature. After 3 days the reaction mixture was concentrated under reduced
10 pressure and the residue added to a column of silica. The mixture was then
chromatographed eluting with dichloromethane then dichloromethane : ethyl acetate (19:1)
to give a solid. This was dissolved in dichloromethane (75 ml) and the solution washed
with aqueous hydrochloric acid (2M, 2 x 30 ml). The organic solution was dried over
anhydrous magnesium sulphate, filtered and concentrated under reduced pressure. The
15 residue was washed with ether : hexane (1:1) to give the title compound as a colourless
solid (0.40 g).

Melting point: 128-130 °C

MS (APCI +ve) 330 (M+H)⁺

20 ¹H NMR (DMSO-d₆) δ 8.81 (1H, s), 7.46 (1H, d), 7.12 (1H, d), 6.65 (1H, dd),
4.04 (2H, s), 3.71 (3H, s), 2.15-2.12 (6H, m), 1.78 (6H, d), 1.7-1.5 (6H, m).

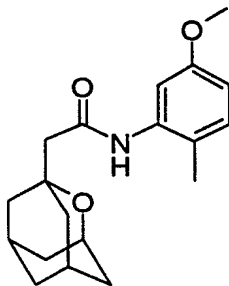
Example 47***N*-(5-Methoxy-2-methylphenyl)-(3-bromo-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide**

To a solution of 3-bromoadamantane acetic acid (CN 17768-34-2) (0.123 g) in
5 dichloromethane (5 ml) was added oxalyl chloride (0.5 ml) and resulting reaction mixture
heated to reflux temperature for 2 hr before concentration at reduced pressure. Residue
was dissolved in dichloromethane (5 ml) and a mixture of 5-methoxy-2-methylaniline
(0.062 g) and triethylamine (0.2 ml) in dichloromethane (2 ml) was added dropwise and
reaction mixture stirred at room temperature for 18 hr before being poured into dilute HCl
10 and extracted with diethyl ether. Organic extracts combined, washed with water, 15%
NaOH solution, brine, dried (Na₂SO₄) and concentrated to leave a solid that was triturated
with ether to leave the title compound as a white solid (0.07 g).

Melting point: 133 °C

15 MS (APCI +ve) 392/394 (M+H)⁺

¹H NMR (DMSO-d₆) δ 9.13 (1H, s), 7.09 (1H, d), 7.05 (1H, d), 6.66 (1H, dd),
3.70 (3H, s), 2.28-2.13 (11H, m), 2.18 (2H, s), 1.68-1.55 (6H, m).

Example 48***N*-(5-Methoxy-2-methylphenyl)-(2-oxa-tricyclo[3.3.1.1^{3,7}]decane)-1-acetamide****a) Ethyl (2-oxa-tricyclo[3.3.1.1^{3,7}]decane)-1-acetate**

5 Sodium borohydride (0.093 g) was added to a solution of ethyl 7-oxobicyclo[3.3.1]non-3-ylideneacetate (0.113g, *Chem.Pharm.Bull.*, 1979, 27, 824) in ethanol (2 ml) and the reaction left to stir at room temperature for 3 days. Reaction was diluted with dichloromethane (60 ml) and washed with a saturated solution of aqueous ammonium chloride (20 ml). The organic phase was dried over anhydrous magnesium sulphate, filtered and concentrated under reduced pressure. The residue was purified by
10 column chromatography over silica eluting with dichloromethane and then dichloromethane : ether (9:1) to give the sub-title compound as an oil (0.078 g).

¹H NMR (CDCl₃) δ 4.15 (2H, q), 4.09 (1H, bs), 2.37 (2H, s), 2.16 (2H, bs),
15 2.2-1.5 (10H, m), 1.27 (3H, t).

b) *N*-(5-Methoxy-2-methylphenyl)-(2-oxa-tricyclo[3.3.1.1^{3,7}]decane)-1-acetamide

Aqueous sodium hydroxide (10%, 2 ml) was added to a solution of ethyl (2-oxa-tricyclo[3.3.1.1^{3,7}]decane)-1-acetate (66 mg) in ethanol (2 ml). After stirring at room
20 temperature for 1 hour the solvent was removed under reduced pressure. The residue was partitioned between aqueous hydrochloric acid (2M, 6 ml) and dichloromethane (2 x 20 ml). The organic extracts were dried over anhydrous magnesium sulphate, filtered and concentrated under reduced pressure to give (2-oxa-tricyclo[3.3.1.1^{3,7}]decane)-1-acetic acid. Thionyl chloride (3 ml) was added to the acid and the reaction heated at reflux for 2
25 minutes. The excess thionyl chloride was removed by concentration under reduced

pressure and the residue was then dissolved in dichloromethane (5 ml). This solution was then added over 1 minute to a solution of 5-methoxy-2-methylaniline (69 mg) in dichloromethane (5 ml) and triethylamine (1 ml) at room temperature for 20 minutes. The reaction mixture was diluted with dichloromethane to 60 ml and then washed with aqueous hydrochloric acid (2M, 30 ml). The organic phase was dried over anhydrous magnesium sulphate, filtered and concentrated under reduced pressure. The residue was purified by column chromatography over silica eluting with dichloromethane then dichloromethane : ether (19:1) to give, after trituration with iso-hexane, a colourless solid (0.05 g).

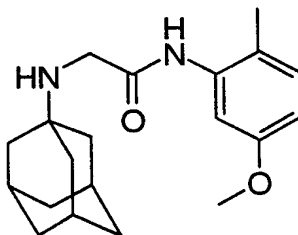
Melting point: 108-109.5 °C

MS (APCI +ve) 316 (M+H)⁺

¹H NMR (DMSO-d₆) δ 9.12 (1H, s), 7.39 (1H, d), 7.08 (1H, d), 6.61 (1H, dd), 4.09 (1H, bs), 3.69 (3H, s), 2.37 (2H, s), 2.15-2.05 (2H, m), 2.13 (3H, s), 1-9-1.55 (10H, m).

Example 49

N-(5-Methoxy-2-methylphenyl)-2-(tricyclo[3.3.1.1^{3,7}]decan-1-amino)acetamide



a) *N*-(5-Methoxy-2-methylphenyl)-2-chloroacetamide

To a solution of 5-methoxy-2-methylaniline (7.62 g) and triethylamine (15.5 ml) in dichloromethane (150 ml) at 0-5 °C was added chloroacetyl chloride (5.0 ml) dropwise and the ice bath removed. The resulting reaction mixture was stirred for 45 min before being poured into dil HCl and extracted with dichloromethane. Organic extracts were combined, washed with water, dried (Na₂SO₄) and concentrated to give a brown solid that was triturated with diethyl ether to leave the sub-title compound as a beige solid (5.7 g).

Melting point: 89-91 °C

¹H NMR (DMSO-d₆) δ 9.58 (1H, s), 7.12 (1H, d), 7.05 (1H, d), 6.71 (1H, dd), 4.30 (2H, s), 3.71 (3H, s), 2.13 (3H, s).

b) N-(5-Methoxy-2-methylphenyl)-2-(tricyclo[3.3.1.1^{3,7}]decan-1-amino)acetamide

5 A solution of chloroamide from step a) (0.092 g), adamantanamine (0.13g), diisopropylethylamine (0.17ml) and tetrahydrofuran (1.5 ml) was heated in a sealed Wheaton vial to 100 °C for 18 hr. Reaction mixture cooled to room temperature and poured into water and extracted with diethyl ether. Organic extracts combined, washed with brine, dried (Na₂SO₄) and concentrated and residue purified by column
10 chromatography over silica eluting 0-2% methanol in dichloromethane to give the title compound as a white solid (0.034 g).

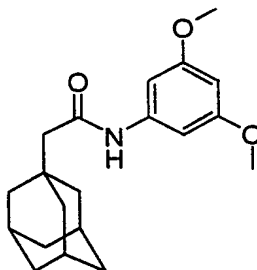
Melting point: 158 °C

MS (APCI +ve) 329 (M+H)⁺

15 ¹H NMR (DMSO-d₆) δ 9.92 (1H, s), 7.76 (1H, d), 7.10 (1H, d), 6.57 (1H, dd), 3.69 (3H, s), 3.22 (2H, s), 2.27 (1H, br s), 2.18 (3H, s), 2.01 (3H, s), 1.58 (12H, s).

Example 50

N-(3,5-Dimethoxyphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide



20 Prepared according to the method of Example 39 from 1-adamantaneacetic acid (3.0 g) and 3,5-dimethoxyaniline (3.0 g) to give the title compound as a white solid (4.2 g).

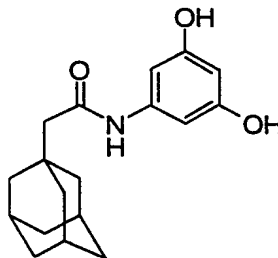
Melting point: 144-146 °C

25 MS (APCI +ve) 330 (M+H)⁺

^1H NMR (DMSO- d_6) δ 9.69 (1H, s), 6.86 (2H, d), 6.18 (1H, t), 3.70 (6H, s), 2.02 (2H, s), 1.93 (3H, s), 1.68-1.57 (12H, m).

Example 51

5 *N*-(3,5-Dihydroxyphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide

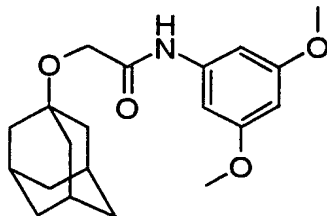


To a solution of *N*-(3,5-dimethoxyphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide (2.22 g) in dichloromethane (200 ml) at -78 °C was added boron tribromide (60 ml of a 1M solution in dichloromethane). Cooling bath was removed and reaction stirred at room
10 temperature for 3 days. Reaction was quenched by addition of ice (230 g). After stirring vigorously for 30 min ethyl acetate (700 ml) added and the organic layer separated, dried (MgSO_4) and concentrated. The residue was purified by column chromatography over silica eluting 5% ethanol in dichloromethane to give the leave a white solid (1.95 g). A portion of this was recrystallised from hot ethyl acetate to leave the title compound as an
15 off-white solid.

Melting point: 239-242 °C

MS (APCI +ve) 302 ($\text{M}+\text{H}$)⁺

^1H NMR (DMSO- d_6) δ 9.42 (1H, s), 9.09 (2H, s), 6.55 (2H, d), 5.87 (1H, t), 1.99 (2H, s),
20 1.92 (3H, s), 1.69-1.56 (12H, m).

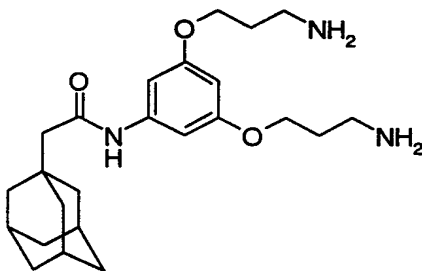
Example 52***N*-(3,5-Dimethoxyphenyl)-tricyclo[3.3.1.1^{3,7}]decanyloxy-1-acetamide**

Prepared according to the method of Example 46 using 1-adamantyloxyacetic acid (2.0 g) and 3,5-dimethoxyaniline (1.75 g) to leave the title compound as an oil (2.5 g).

MS (APCI +ve) 346 (M+H)⁺

¹H NMR (DMSO-d₆) δ 9.23 (1H, s), 6.94 (2H, s), 6.23 (1H, s), 3.98 (2H, s), 3.71 (6H, s), 2.12 (3H, s), 1.76(6H, d), 1.59 (6H, m).

10

Example 53***N*-(3,5-Bis-(3-aminopropoxy)phenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide**

Prepared according to the method of Example 2 using *N*-(3,5-dihydroxyphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide from Example 51 (0.60 g), *tert*-butyl *N*-(3-hydroxypropyl)carbamate (1.43 g), tributylphosphite (2.0 ml) and 1,1'(azodicarbonyl)dipiperidine (2.05 g) to leave the title compound as a fawn solid (0.12 g).

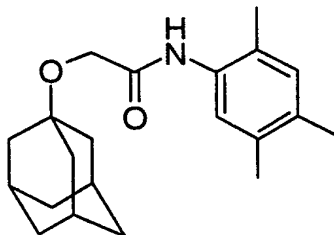
MS (APCI +ve) 416 (M+H)⁺

¹H NMR (DMSO-d₆) δ 9.81 (1H, s), 8.00 (6H, br s), 6.91 (2H, d), 6.22 (1H, t), 4.00 (4H, t), 2.93 (4H, t), 2.04-1.98 (9H, m), 1.69-1.56 (12H, m).

20

Example 54

***N*-(2,4,5-Trimethylphenyl)-tricyclo[3.3.1.1^{3,7}]decanyloxy-1-acetamide**



The title compound was prepared as in Example 46 from 2,4,5-trimethylaniline
5 (0.30 g) and 1-adamantyloxyacetic acid (0.38 g, CA 1966, 65, 2149a) as a colourless solid (0.41 g).

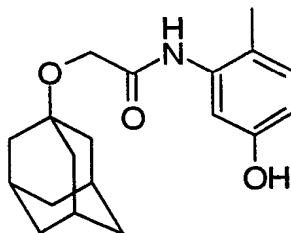
Melting point: 138-140 °C

MS (APCI +ve) 328 (M+H)⁺

10 ¹H NMR (DMSO-d₆) δ 8.76 (1H, s), 7.42 (1H, s), 6.98 (1H, s), 4.00 (2H, s),
2.2-2.1 (12H, m), 1.8-1.75 (6H, m), 1.65-1.55 (6H, m).

Example 55

***N*-(5-Hydroxy-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decanyloxy-1-acetamide**



15

Thionyl chloride (5 ml) was added to 1-adamantyloxyacetic acid (2.00 g, CA 1966, 65, 2149a) and the reaction heated at reflux for 5 minutes. The excess thionyl chloride was removed by concentration under reduced pressure and the residue was then dissolved in dichloromethane (10 ml). This solution was then added over 5 minutes to a solution of
20 2-methyl-5-hydroxyaniline hydrochloride (1.00 g *J.Chem.Soc. Perkin Trans. 2*, 1972, 539) in dichloromethane (20 ml) and triethylamine (10 ml) at 0 °C. The solution was then allowed to warm to room temperature and, after 30 minutes stirring, was concentrated

under reduced pressure. The residue was dissolved in methanol (20 ml) and tetrahydrofuran (10 ml) and was treated with a solution of sodium methoxide in methanol (25 wt.%, 10 ml). After 15 minutes stirring the reaction was treated with formic acid (4 ml) and then concentrated under reduced pressure. The residue was partitioned between aqueous hydrochloric acid (2M, 90 ml), ethyl acetate (90 ml) and tetrahydrofuran (50 ml). The organic phase was separated, washed with saturated aqueous sodium chloride (50 ml), dried over anhydrous magnesium sulphate, filtered and concentrated under reduced pressure to give a solid (2.62 g). This was purified by column chromatography over silica eluting with dichloromethane : ethyl acetate (4:1) to give a colourless solid (1.39 g).

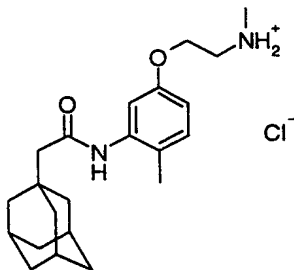
Melting point: 258 °C (dec.)

MS (APCI +ve) 316 (M+H)⁺

¹H NMR (DMSO-d₆) δ 9.22 (1H, s), 8.71 (1H, s), 7.37 (1H, d), 6.98 (1H, d), 6.45 (1H, dd), 4.02 (2H, s), 2.13(3H, bs), 2.10 (3H, s), 2.15-2.12 (6H, m), 1.78 (6H, d), 1.7-1.5 (6H, m).

Example 56

N-(5-(2-(*N*-Methylamino)ethoxy)-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide, hydrochloride



Tert-butyl-*N*-(2-hydroxyethyl)-*N*-methylcarbamate (1.05 g, Synth. Commun., 1993, 23(17), 2443), *N*-(5-hydroxy-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide (1.00 g, Example 12), tetrahydrofuran (40 ml) and tributylphosphine (1.35 ml) were combined, cooled in ice/water, before addition of 1,1'-(azodicarbonyl)dipiperidine (1.39 g) and reaction stirred for 10 minutes. After stirring at room temperature for 90 minutes further

tert-butyl *N*-(2-hydroxyethyl)-*N*-methylcarbamate (1.04 g) and tributylphosphine (1.35 ml) were added and the solution recooled in ice/water before addition of 1,1'-(azodicarbonyl)dipiperidine (1.39 g) and stir in ice/water for 10 minutes then at room temperature overnight. The reaction mixture was diluted with iso-hexane (50 ml) and filtered. The residue was washed with ether (100 ml) and the combined organics concentrated under reduced pressure. The residue was purified by column chromatography over silica eluting with iso-hexane : ethyl acetate (7:3) and further purified by column chromatography over silica eluting with dichloromethane : ethyl acetate (9:1) to give the coupled product (0.57 g) which was dissolved in methanol (10 ml). A solution of hydrogen chloride (generated by slow addition of acetyl chloride (10 ml) to methanol (15 ml) at 0°C **CARE - Very Exothermic**) was then added to the latter solution and the reaction stirred at room temperature for 2 hours. The reaction was then concentrated under reduced pressure and then triturated with ether (100 ml) give the title compound as colourless solid (0.35 g).

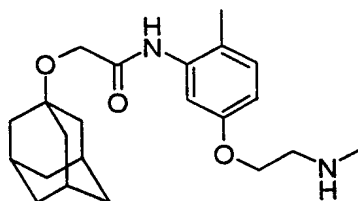
Melting point: 193-195 °C

MS (APCI +ve) 357 (M+H)⁺ as free base

¹H NMR (DMSO-d₆) δ 9.06 (1H, s), 8.91 (2H, bs), 7.19 (1H, d), 7.12 (1H, d), 6.70 (1H, dd), 4.17 (2H, t), 3.4-3.25 (2H, m), 2.61 (3H, s), 2.15 (3H, s), 2.11 (2H, s), 1.95 (3H, s), 1.75-1.55 (12H, m).

Example 57

N-(5-(2-(*N*-Methylamino)ethoxy)-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decanyloxy-1-acetamide



a) *N*-(5-Hydroxy-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decanyloxy-1-acetamide

Thionyl chloride (5 ml) was added to 1-adamantyloxyacetic acid (2.00 g, CA 1966, 65, 2149a) and the reaction heated at reflux for 5 minutes. The excess thionyl chloride was

removed by concentration under reduced pressure and the residue was dissolved in dichloromethane (10 ml). This solution was added over 5 minutes to a solution of 5-hydroxy-2-methylaniline, hydrochloride (1.00 g *J.Chem.Soc. Perkin Trans. 2*, 1972, 539) in dichloromethane (20 ml) and triethylamine (10 ml) at 0 °C. The solution was allowed to warm to room temperature and, after 30 minutes stirring, was concentrated under reduced pressure. The residue was dissolved in methanol (20 ml) and tetrahydrofuran (10 ml) and was treated with a solution of sodium methoxide in methanol (25 wt.%, 10 ml). After 15 minutes stirring the reaction was treated with formic acid (4 ml) and concentrated under reduced pressure. The residue was partitioned between aqueous hydrochloric acid (2M, 90 ml), ethyl acetate (90 ml) and tetrahydrofuran (50 ml). The organic phase was separated, washed with saturated aqueous sodium chloride (50 ml), dried over anhydrous magnesium sulphate, filtered and concentrated under reduced pressure. The residue was purified by column chromatography over silica eluting with dichloromethane : ethyl acetate (4:1) to give the sub-title compound as a colourless solid (1.39 g).

15

Melting point: 258 °C (dec.)

MS (APCI +ve) 316 (M+H)⁺

¹H NMR (DMSO-d₆) δ 9.22 (1H, s), 8.71 (1H, s), 7.37 (1H, d), 6.98 (1H, d), 6.45 (1H, dd), 4.02 (2H, s), 2.13(3H, bs), 2.10 (3H, s), 2.15-2.12 (6H, m), 1.78 (6H, d), 1.7-1.5 (6H, m).

20

b) N-(5-(2-(N-Methylamino)ethoxy)-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]-decanyloxy-1-acetamide

Prepared using the method described in Example 2 using tert-butyl N-(2-hydroxyethyl)-N-methylcarbamate (1.05 g, *Synth. Commun.*, 1993, 23(17), 2443) and N-(5-hydroxy-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decanyloxy-1-acetamide (1.00 g, part a) to give the title compound as a colourless solid (0.54 g).

25

Melting point: 155-158 °C (dec.)

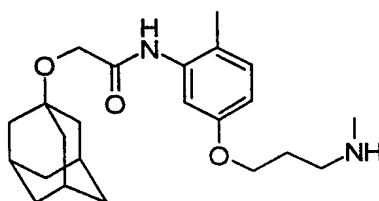
MS (APCI +ve) 373 (M-HCl+H)⁺

30

^1H NMR (DMSO- d_6) δ 9.07 (2H, bs), 8.84 (1H, s), 7.57 (1H, d), 7.16 (1H, d), 6.71 (1H, dd), 4.20 (2H, t), 4.05 (2H, s), 3.30 (2H, t), 2.60 (3H, t), 2.17 (3H, s), 2.13 (3H, s), 1.78 (6H, d), 1.65-1.55 (6H, m).

5 **Example 58**

***N*-(5-(3-(*N*-Methylamino)propyloxy)-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decanyloxy-1-acetamide**



Prepared using the method described in Example 56 from *tert*-butyl *N*-(3-hydroxypropyl)-*N*-methylcarbamate (1.01 g, J. Org. Chem., 1988, 53(10), 2229) and *N*-(5-hydroxy-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decanyloxy-1-acetamide (1.00 g, Example 55) to give the title compound as a colourless solid (0.50 g).

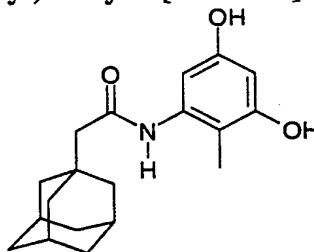
Melting point: 151-154 °C (dec.)

15 MS (APCI +ve) 387 (M-HCl+H)⁺

^1H NMR (DMSO- d_6) δ 8.91 (2H, bs), 8.82 (1H, s), 7.49 (1H, d), 7.13 (1H, d), 6.67 (1H, dd), 4.04 (2H, s), 4.01 (2H, t), 3.03 (2H, quintet), 2.55 (3H, t), 2.15 (3H, s), 2.13 (3H, s), 2.06 (2H, quintet), 1.78 (6H, d), 1.65-1.55 (6H, m).

20 **Example 59**

***N*-(3,5-Dihydroxy-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decane-acetamide**



A solution of dimethoxy ether from Example 43 (2.0 g) in 50% hydrobromic acid in acetic acid was heated at 100 degrees for 12 hours. The solution was concentrated under vacuum, the residue taken in water and extracted with ethyl acetate. The organic layers were dried over magnesium sulfate, filtered, concentrated under vacuum. The crude material was purified over silica eluting with dichloromethane/ethyl acetate to afford the title compound as a white solid.

Melting point: 270 °C (dec.)

MS (APCI +ve) 316 (M+H)⁺

¹H NMR (CDCl₃) δ 9.09(1H, s); 8.91(1H, s); 8.86(1H, bs); 6.35(1H, d); 6.11(4H, d); 2.04(2H, s); 1.94(3H, bs); 1.87(3H, s); 1.80-1.50(12H, m).

Example 60

Pharmacological Analysis

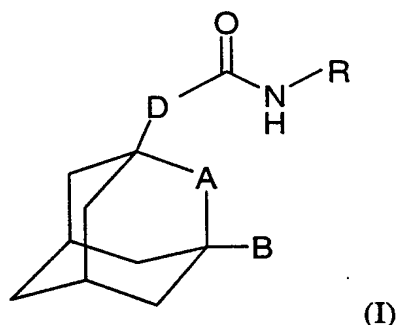
Certain compounds such as benzoylbenzoyl adenosine triphosphate (bbATP) are known to be agonists of the P2X₇ receptor, effecting the formation of pores in the plasma membrane (Drug Development Research (1996), 37(3), p.126). Consequently, when the receptor is activated using bbATP in the presence of ethidium bromide (a fluorescent DNA probe), an increase in the fluorescence of intracellular DNA-bound ethidium bromide is observed. The increase in fluorescence can be used as a measure of P2X₇ receptor activation and therefore to quantify the effect of a compound on the P2X₇ receptor.

In this manner, each of the title compounds of Examples 1 to 59 were tested for antagonist activity at the P2X₇ receptor. Thus, the test was performed in 96-well flat bottomed microtitre plates, the wells being filled with 250 µl of test solution comprising 200 µl of a suspension of THP-1 cells (2.5 x 10⁶ cells/ml) containing 10⁻⁴ M ethidium bromide, 25 µl of high potassium buffer solution containing 10⁻⁵ M bbATP, and 25 µl of high potassium buffer solution containing 3 x 10⁻⁵ M test compound. The plate was covered with a plastics sheet and incubated at 37 °C for one hour. The plate was then read in a Perkin-Elmer fluorescent plate reader, excitation 520 nm, emission 595 nm, slit widths: Ex 15 nm, Em 20 nm. For the purposes of comparison, bbATP (a P2X₇ receptor

agonist) and pyridoxal 5-phosphate (a P2X₇ receptor antagonist) were used separately in the test as controls. From the readings obtained, a pIC₅₀ figure was calculated for each test compound, this figure being the negative logarithm of the concentration of test compound necessary to reduce the bbATP agonist activity by 50%. Each of the compounds of
5 Examples 1 to 59 demonstrated antagonist activity, having a pIC₅₀ figure > 4.50.

CLAIMS

1. A compound of general formula



- 5 wherein A represents a group CH_2 or an oxygen atom;
 B represents a hydrogen or halogen atom;
 D represents a group CH_2 , OCH_2 , NHCH_2 or CH_2CH_2 ;
 R represents a phenyl, benzothiazolyl, indolyl, indazolyl, purinyl, pyridyl, pyrimidinyl or
 thiophenyl group, each of which may be optionally substituted by one or more substituents
 10 independently selected from a halogen atom or a cyano, carboxyl, hydroxyl, nitro,
 halo- C_1 - C_6 -alkyl, $-\text{N}(\text{R}^1)-\text{C}(=\text{O})-\text{R}^2$, $-\text{C}(\text{O})\text{NR}^3\text{R}^4$, $-\text{NR}^5\text{R}^6$, C_3 - C_8 -cycloalkyl,
 3- to 8-membered heterocyclyl, C_3 - C_8 -cycloalkyloxy, C_1 - C_6 -alkylcarbonyl, phenoxy,
 benzyl, C_1 - C_6 -alkylthio, phenylthio, C_1 - C_6 -alkoxycarbonyl, C_1 - C_6 -alkylsulphinyl or
 C_1 - C_6 -alkylsulphonyl group, or a C_1 - C_6 -alkyl or C_1 - C_6 -alkoxy group optionally
 15 substituted by one or more substituents independently selected from a halogen atom or an
 amino, carboxyl, hydroxyl, C_1 - C_6 -alkoxy, (di) C_1 - C_6 -alkylamino,
 C_1 - C_6 -alkoxycarbonyl, imidazolyl, morpholinyl, piperidinyl or pyrrolidinyl group;
 R^1 represents a hydrogen atom or a C_1 - C_6 -alkyl or C_3 - C_8 -cycloalkyl group;
 R^2 represents a C_1 - C_6 -alkyl or C_3 - C_8 -cycloalkyl group; and
 20 R^3 , R^4 , R^5 and R^6 each independently represent a hydrogen atom or a C_1 - C_6 -alkyl or
 C_3 - C_8 -cycloalkyl group;
 with the provisos that when A is CH_2 , B is H and D is CH_2 , then R does not represent a
 phenyl, ortho-carboxyphenyl, methylphenyl or para-phenoxyphenyl group, and that when A
 is CH_2 , D is CH_2 or CH_2CH_2 and R represents a substituted phenyl group, the
 25 substituent or substituents present do not comprise, in an ortho position, a C_1 - C_6 -alkoxy

group substituted by an amino, (di)C₁-C₆-alkylamino, imidazolyl, morpholinyl, piperidinyl or pyrrolidinyl group;
or a pharmaceutically acceptable salt or solvate thereof.

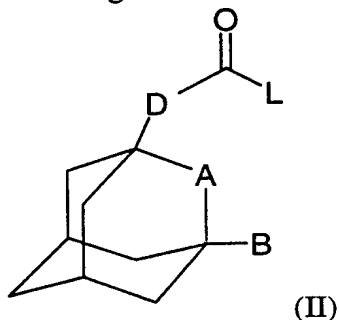
- 5 2. A compound according to claim 1, wherein A represents a group CH₂.
3. A compound according to claim 1 or claim 2, wherein B represents a hydrogen atom.
4. A compound according to any one of claims 1 to 3, wherein D represents a group
10 CH₂, OCH₂ or NHCH₂.
5. A compound according to any one of claims 1 to 4, wherein R represents a phenyl, benzothiazolyl, indolyl, indazolyl, purinyl, pyridyl or thiophenyl group, each of which may be optionally substituted by one, two or three substituents independently selected from a
15 halogen atom or a hydroxyl, nitro or C₁-C₄-alkoxycarbonyl group, or a C₁-C₄-alkyl or C₁-C₄-alkoxy group optionally substituted by one or two substituents independently selected from a halogen atom or an amino, carboxyl, hydroxyl, C₁-C₄-alkoxy, (di)C₁-C₄-alkylamino, C₁-C₄-alkoxycarbonyl, imidazolyl, morpholinyl, piperidinyl or pyrrolidinyl group.
- 20 6. A compound of formula (I) as defined in claim 1, or a pharmaceutically acceptable salt or solvate thereof, being:
- N*-(2-Methyl-6-benzothiazolyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
N-(3-(3-(Aminopropoxy)-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
25 hydrochloride,
N-(2-Chlorophenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
N-(2,4,5-Trimethylphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
N-(5-Methoxy-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
N-(2,3-Dimethylphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
30 *N*-(5-Indolyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,

- N*-(2,3-Dimethyl-5-indolyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
N-[5-(3-*N,N*-Dimethylaminopropoxy)-2-methylphenyl]-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide, hydrochloride,
N-(5-Indazolyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
5 *N*-(6-Indazolyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
N-(5-Hydroxy-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
N-(1*H*-Indol-4-yl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
4-Methyl-3-[[1-oxo-2-(tricyclo[3.3.1.1^{3,7}]dec-1-yl)ethyl]amino]phenoxy-acetic acid, hydrochloride salt,
10 *N*-(1-Methyl-1*H*-indol-5-yl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
N-(1-(*N,N*-Dimethylamino)ethyl-1*H*-indo-5-yl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
5-[[1-Oxo-2-(tricyclo[3.3.1.1^{3,7}]dec-1-yl)ethyl]amino]-1*H*-indole-1-acetic acid, 1,1-dimethylethyl ester,
N-(3-(2-Chloropyridyl))-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
15 *N*-(3-(*N,N*-Dimethylamino)methyl-1*H*-indo-5-yl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
N-(4-Methoxy-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
N-(2-Chloro-5-methoxyphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
N-(4-Hydroxy-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
N-(3-Hydroxymethyl-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
20 *N*-(5-Methoxy-2-methyl-3-nitrophenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
N-(5-Hydroxymethyl-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
N-(3-Hydroxy-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
N-(2-Methyl-5-(1-pyrrolidinemethyl)phenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide, hydrochloride,
25 *N*-(2-Chloro-5-hydroxyphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
N-(2-Chloro-4-hydroxyphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
N-(2-Methyl-3-(2-(1-pyrrolidino)ethyloxy)phenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide, hydrochloride,
N-(5-Methoxymethyl-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,

- N*-(2-Methyl-3-(2-(1-morpholino)ethyloxy)phenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide, hydrochloride,
- N*-(2-Methyl-3-(2-(1-piperidino)ethyloxy)phenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide, hydrochloride,
- 5 *N*-(2-Methyl-5-(1-morpholinomethyl)phenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide, hydrochloride,
- N*-(5-(3-(2-*N,N*-dimethylaminoethyl)indolyl))-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide, hydrochloride,
- Methyl 4-methyl-3-[[1-oxo-2-(tricyclo[3.3.1.1^{3,7}]dec-1-yl)ethyl]amino]thiophene-2-
- 10 carboxylate,
- N*-(3-Methoxy-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
- N*-(2-Methyl-3-(2-(1-imidazolo)ethyloxy)phenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
- N*-(2,4,6-Trimethylphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
- N*-(5-(3-Aminopropoxy)-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
- 15 hydrochloride,
- N*-(5-(3-(*N*-Methylamino)propoxy)-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide, hydrochloride,
- N*6-(Tricyclo[3.3.1.1^{3,7}]decane-1-acetyl)adenine,
- N*-(3,5-Dimethoxy-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
- 20 *N*-(3-(3-(*N*-Methylamino)propoxy)-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide, hydrochloride,
- N*-(5-(3-(*N,N*-Dimethylamino)propoxy)-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide, hydrochloride,
- N*-(5-Methoxy-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decanyloxy-1-acetamide,
- 25 *N*-(5-Methoxy-2-methylphenyl)-(3-bromo-tricyclo[3.3.1.1^{3,7}]decane)-1-acetamide,
- N*-(5-Methoxy-2-methylphenyl)-(2-oxa-tricyclo[3.3.1.1^{3,7}]decane)-1-acetamide,
- N*-(5-Methoxy-2-methylphenyl)-2-(tricyclo[3.3.1.1^{3,7}]decan-1-amino)acetamide,
- N*-(3,5-Dimethoxyphenyl)-tricyclo[3.3.1.1^{3,7}]decan-1-acetamide,
- N*-(3,5-Dihydroxyphenyl)-tricyclo[3.3.1.1^{3,7}]decan-1-acetamide,
- 30 *N*-(3,5-Dimethoxyphenyl)-tricyclo[3.3.1.1^{3,7}]decanyloxy-1-acetamide,

- N*-(3,5-Bis-(3-aminopropoxy)phenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
N-(2,4,5-Trimethylphenyl)-tricyclo[3.3.1.1^{3,7}]decanyloxy-1-acetamide,
N-(5-Hydroxy-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decanyloxy-1-acetamide,
N-(5-(2-(*N*-Methylamino)ethyloxy)-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-
 5 acetamide, hydrochloride,
N-(5-(2-(*N*-Methylamino)ethyloxy)-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decanyloxy-1-
 acetamide,
N-(5-(3-(*N*-Methylamino)propyloxy)-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decanyloxy-1-
 acetamide, or
 10 *N*-(3,5-Dihydroxy-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decane-acetamide.

7. A process for the preparation of a compound of formula (I) as defined in claim 1 which comprises reacting a compound of general formula



- 15 wherein L represents a leaving group and A, B and D are as defined in formula (I), with a compound of general formula (III), R-NH₂, wherein R is as defined in formula (I); and optionally forming a pharmaceutically acceptable salt or solvate thereof.

8. A pharmaceutical composition comprising a compound of formula (I), or a
 20 pharmaceutically acceptable salt or solvate thereof, as claimed in any one of claims 1 to 6 in association with a pharmaceutically acceptable adjuvant, diluent or carrier.

9. A process for the preparation of a pharmaceutical composition as claimed in claim 8 which comprises mixing a compound of formula (I), or a pharmaceutically acceptable salt

or solvate thereof, as defined in any one of claims 1 to 6 with a pharmaceutically acceptable adjuvant, diluent or carrier.

10. A compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof,
5 as claimed in any one of claims 1 to 6 for use in therapy.
11. A compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof,
as claimed in any one of claims 1 to 6 for use in the treatment of rheumatoid arthritis.
- 10 12. Use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate
thereof, as claimed in any one of claims 1 to 6 in the manufacture of a medicament for use
in therapy.
13. A method of effecting immunosuppression which comprises administering to a
15 patient a therapeutically effective amount of a compound of formula (I), or a
pharmaceutically acceptable salt or solvate thereof, as claimed in any one of claims 1 to 6.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 98/02189

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: C07C 233/25, C07D 209/04, C07D 231/54, C07D 277/62, C07D 221/22,
A61K 31/16, A61K 31/40, A61K 31/415, A61K 31/425, A61K 31/445

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: C07C, C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Journal of Medical Chemistry, Volume 15, No 11, 1972, V.L. Narayanan, "Adamantyl Analogs of 2'-(3-Dimethylaminopropylthio)cinnamanilide" page 1180 - page 1182 --	1-13
X	EP 0395093 A1 (KYOWA HAKKO KOGYO CO., LTD.), 31 October 1990 (31.10.90), compounds 109 and 128 --	1-10,12
X	STN International, File CAPLUS, CAPLUS accession no. 1975:592744, Document no. 83:192744, Kreutzberger, A. et al: "Antiviral agents. 4. Aromatically substituted carbonic acid amide structure in potentially virustatic compounds"; Arzneim.-Forsch. (1975), 25(7), 994-7 --	1-5,7-10,12

☒ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"I" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

24 March 1999

Date of mailing of the international search report

30 MAR 1999

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 98/02189

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 3789072 A (JACK BERNSTEIN), 29 January 1974 (29.01.74), ex 15 and 16 --	1-5,7-10,12
X	STN International, File CAPLUS, CAPLUS accession no. 1974:26871, Document no. 80:26871, Danilenko, G.I. et al "Synthesis and biological activity of adamantane derivatives. II. N-(1-Adaman- toyl)anthranilic acids"; Khim.-Farm. Zh. (1973), 7(10), 15-17 --	1-2,7-10,12
X	STN International, File CAPLUS, CAPLUS accession no. 1968:402562, Document no. 69:2562, Sasaki, Tadashi et al: "Synthesis of adamantane derivatives II. Preparation of some derivatives from adamantylacetic acid"; Bull. Chem. Soc. Jap. (1968), 41(1), 238-40 --	1-3,5
A	STN International, File CAPLUS, CAPLUS accession no. 1975:3853, Document no. 82:3853, Kreutzberger, A. et al: "Antiviral agents. 3. Aliphatic acid amide grouping as partial structure in virustatics; Arch. Pharm. (Weinheim, Ger.) (1974), 307(10), 766-74 --	1-12
A	Tetrahedron, Volume 44, No 23, 1988, M.S. Syamala et al, "Modification of Photochemical Reactivity by Cyclodextrin Complexation: Product Selectivity in Photo-Fries Rearrangement", page 7234 - page 7242, compounds 10 and 14, page 7235 -- -----	1-5

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 98/02189

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 13
because they relate to subject matter not required to be searched by this Authority, namely:

Claim 13 relates to a method of treatment of the human or animal body by surgery or by therapy (Rule 39.1(iv)). Nevertheless, a search has been executed for this claim. The search has been based on the alleged effects of the compounds.
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐

The additional search fees were accompanied by the applicant's protest.

☐

No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/SE 98/02189

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0395093 A1	31/10/90	CA 2015473 A,C DE 69002996 D,T JP 2749951 B JP 3215461 A US 5112867 A US 5413997 A	28/10/90 24/03/94 13/05/98 20/09/91 12/05/92 09/05/95
US 3789072 A	29/01/74	NONE	